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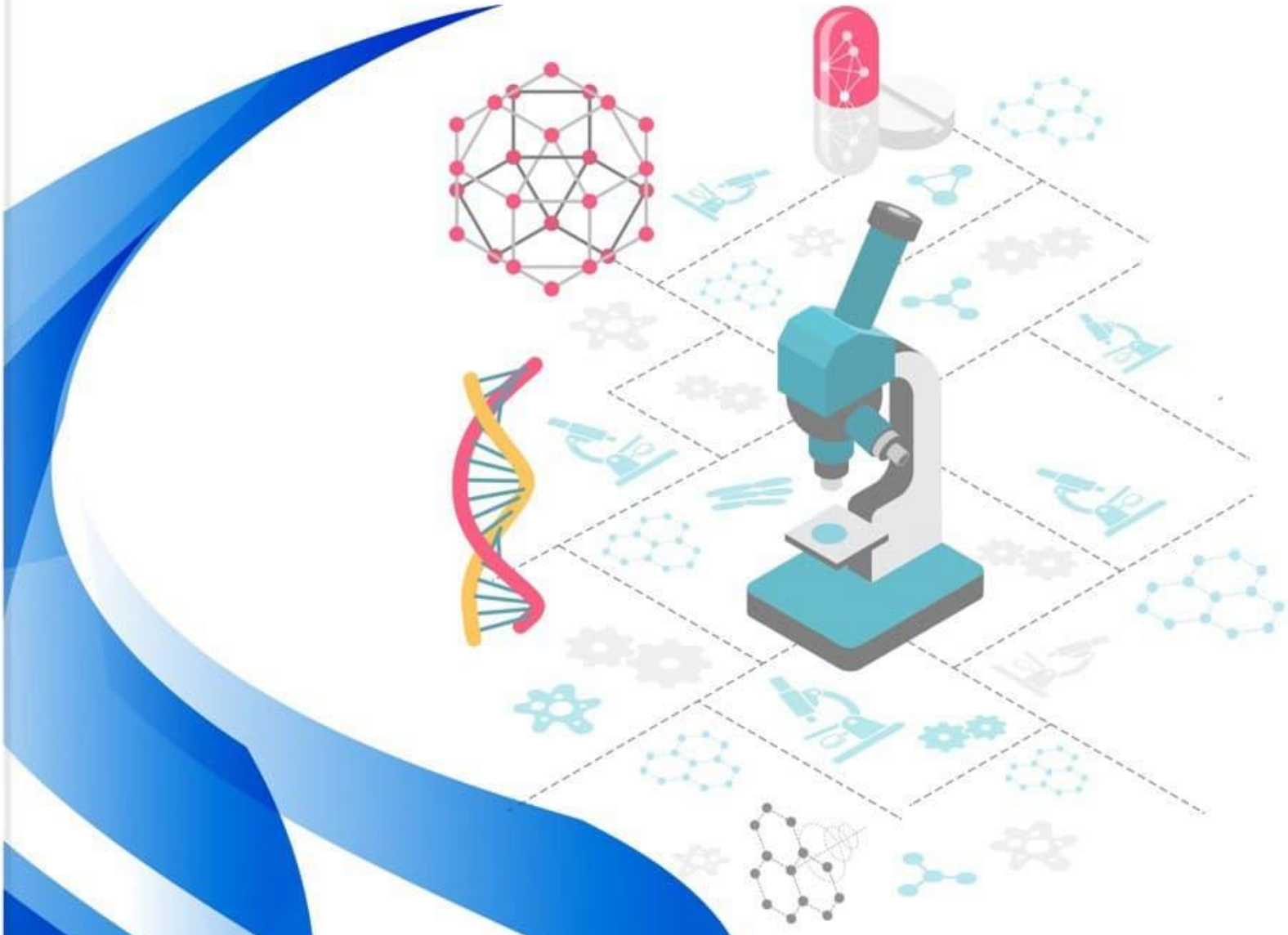

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CORONAVIRUS INFECTION AN OBESE PATIENT

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Abstract. In the modern world, the problem of obesity against the background of the pandemic of a new coronavirus infection has become particularly dangerous. On the one hand, the prevalence of obesity among the population is steadily increasing, on the other hand, it has been proven that obese people belong to the most vulnerable group in terms of an increased risk of infection and an unfavorable prognosis. This is due to the presence and peculiarities of the development of various pathological mechanisms in this category of patients. These include high expression of angiotensin converting enzyme 2, a high probability of developing a "cytokine storm", maintenance of a chronic inflammatory process in adipose tissue, changes in the activity of the enzyme dipeptidyl peptidase-4, which lead to an aggravation of metabolic disorders in adipose tissue, as well as impaired immune protection. The severity of the condition of obese patients hospitalized with COVID-19 (COronaVIrus Disease 2019) is due to the presence of polymorbidity. World medical practice in the fight against the COVID-19 pandemic shows that patients with coronavirus infection on the background of obesity more often require hospitalization in intensive care units and connection to artificial ventilation devices. Currently, the features of the course of coronavirus infection against the background of obesity continue to be studied. These include the presence of severe respiratory failure, a high risk of developing respiratory distress syndrome, thrombosis and thromboembolic complications, as well as worsening of the course of chronic cardiovascular diseases, which leads to the development of multiple organ failure and death. The development of drugs takes into account the mechanisms of virus penetration into the cell, the peculiarities of its pathophysiology and interaction with the human body.

Keywords: obesity, coronavirus infection, angiotensin converting enzyme, cytokine storm, respiratory distress syndrome.

Introduction. The problem of obesity existed before the COVID-19 pandemic (COronaVIrus Disease 2019). Currently, obesity is recognized as one of the most serious diseases leading to early disability and high mortality [1]. According to the World Health Organization (WHO, 2016), OH occurs in about 13% of the adult population of the planet (11% of men and 15% of women) [2].

According to the results of the study "Epidemiology of cardiovascular diseases in the regions of the Russian Federation" (ESSAY-RF), the prevalence of obesity among the adult population in 2014 was 29.7±0.3% (30.8±0.4% for women, 26.6±0.5% for men) [3]. Currently, about half (51.7% of women and 46.5% of men) of the Russian population suffers from excess body weight and obesity [4], while the number of patients with this pathology is constantly increasing [5]. A significant feature of our country is a significant increase in the prevalence of LV in men of

working age, which is very significant, since it increases the degree of cardiovascular risk.

It has been proven that patients with LV are most at risk of contracting various infectious diseases with a complicated course [2]. Thus, in the examination of 268 patients hospitalized with influenza A (H1N1) in California, it was shown that 58% of them were diagnosed with LV, and the presence of morbid obesity (body mass index (BMI) ≥40 kg/m2) was associated with a fatal outcome. Another Mexican study also confirmed a higher risk of hospitalization in the presence of OJ not only in influenza, but also in other viral diseases such as parainfluenza, rhinovirus and metapneumovirus infections, as well as coronavirus infection [6].

In the modern world, the problem of a combination of OH and a new coronavirus infection (KIWI) is of particular importance. The COVID-19 epidemic began in December 2019 in the city of Wuhan (China) and has acquired the scale of an emergency situation, spreading at lightning speed to almost all countries of the world. The cause was the new coronavirus MERS-CoV-2, which causes severe Acute Respiratory syndrome (Severe Acute Respiratory Syndrome Coronavirus 2).

The real COVID-19 pandemic has captured the population of Europe and North America, where the prevalence of OH is so high that it can be defined as a "non-infectious epidemic of the XXI century" [7].

The World Health Organization states that already in May 2020, more than 4 million confirmed cases of COVID-19 were registered in the world, among them 280 thousand deaths. According to the information of the official electronic information resource https://coronavirus-monitor.info As of January 2021, the coronavirus disease pandemic (COVID-19) is occurring with the involvement of 96 million cases and 2 million deaths, while in Russia on this date there are 3.6 million people with deaths in 67 thousand patients.

One of the reasons for the increased risk of CVI consequences in acute respiratory failure is the activity of angiotensin converting enzyme 2 (ACE2) [8, 9]. It has been established that overweight activates the expression of gene regions responsible for the formation of ACE 2 protein [10, 11]. It is this protein that is the "entrance gate" through which the SARSCoV-2 virus enters the cell. ACE 2 is involved in the regulation of blood pressure (BP) by inhibiting the activity of the renin-angiotensin system, vasodilation, increased natriuresis and suppression of the activity of the inflammatory process. ACE 2 is also a SARS-CoV-2 receptor, interacting with amino acid transporters and integrins [11]. ACE 2 expression occurs mainly in smooth muscle cells, endothelial cells, pancreatic acinuses, renal tubular epithelium, and adipocytes [12-14]. In adipose tissue, adipocytes themselves and other cells (stromal cells, endothelial cells, macrophages and lymphocytes) can serve as targets for viruses [15]. An analysis of the risk of infection with various viruses in the population showed a low prevalence of SARS-CoV-2 in OJ [16], however, taking into account the high affinity for receptors on target cells, including adipocytes, it is

possible to assume a hematogenic pathway of spread in adipose tissue, which increases the risk of disease in this cohort of patients.

It is significant that men are characterized by a higher level of ACE 2 expression. This feature determines an increased risk of COVID-19 disease due to the higher actual body fat content in the presence of COOLANT [17]. According to literature data, among 41 patients hospitalized for verified COVID-19 in China, 73% of cases were male [18]. A similar pattern was demonstrated by an analysis of the gender composition of patients in the United States, where male patients (12.2%) prevailed among patients with severe coronavirus infection (16%).

The increased risk of severe consequences of COVID-19 in people with OJ is also determined by a higher probability of developing a "cytokine storm". A cytokine storm is an uncontrolled and non—protective reaction of the immune system against healthy tissues. To date, the term "cytokine storm" does not have a generally accepted definition, but only refers to the development of an overactive immune response, which is characterized by excessive release of interferons, interleukins, chemokines, tumor necrosis factor, colony stimulating factor and a number of other mediators that are part of the immune response necessary to effectively counteract pathogens of infectious diseases. This uncontrolled surge in the synthesis of proinflammatory mediators is also called hypercytokinemia and cytokine cascade [19, 21].

It has been established that coolant and metabolic syndrome are accompanied by the production of proinflammatory cytokines and an increase in acute phase proteins, which is caused by chronic inflammation. Patients with LV have higher activity of nuclear transcription factor (NF-kB) and intensive production of proinflammatory cytokines such as tumor necrosis factor α (TNF), interleukin-1 (IL-1) and interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin 10 (IL-10), an inhibitor of plasminogen activator (PAI-1) — factors actively synthesized by adipocytes against the background of COOLANT [20]. OJ is characterized by a violation of innate and acquired immunity, central and peripheral meta-inflammation (chronic systemic inflammation). Cellular hypoxia, mechanical stress of adipocytes, excessive content of free fatty acids and lipopolysaccharides are the main initiators of the site of inflammation [22, 23].

In cytokine storm, a wide range of diverse clinical and laboratory abnormalities are observed, characterizing a generalized systemic inflammatory response. In the respiratory tract, this can be manifested by the development of severe pneumonia, pulmonary edema, acute respiratory distress syndrome (ARDS), severe hypoxemia. In severe cytokine storm, renal and hepatic insufficiency, cholestasis, and cardiomyopathy may develop. The combination of renal failure, endothelial cell death and hypoalbuminemia can lead to a systemic increase in capillary permeability and the development of edematous syndrome. Neurological toxic effects of cytokine storm are often delayed and manifest as encephalopathy of varying severity [21, 24].

SARS-CoV-2 leads to the activation of monocytes, macrophages and dendritic cells, the release of IL-6, which activates cis signals and pleiotropic effects from the

immune system. In a randomized multicenter study, IL-6 was demonstrated to be a strong independent predictor of deaths in COVID-19. Adipose tissue by its nature is the main source of IL-6 and its IL-6R receptor [25]. The ability of the coronavirus to "cling" to IL-6 and its receptors has been established, which ensures the cascading transmission of viral signals and effects.

A large volume of adipose tissue itself is a constant source of proinflammatory cytokines synthesized by both adipocytes themselves and macrophages that have emigrated to adipose tissue, which leads, as already mentioned, to the formation and maintenance of a chronic sluggish inflammatory process in the body. In turn, pathological secretion of adipokines in adipose tissue (IL-1, IL-6, TNFa) in combination with an increase in C-reactive protein, leptin-adiponectin ratio and a decrease in the content of protective factors (adiponectin, anti-inflammatory cytokine IL-10) are accompanied by a deterioration in the immune response and adverse effects on all organs and tissues, including the pulmonary parenchyma and bronchi [26, 27]. It has been established that the increase in proinflammatory biomarkers is directly dependent on the severity of LV. Endocrine dysfunction in abdominal coolant with the accumulation of visceral fat, including pericardial and perivascular, creates prerequisites for the development of the inflammatory process, which plays an essential role in comorbid pathology.

Local and systemic pathological disorders caused by inflammation of adipose tissue (LVT) are primarily caused by intracellular inflammatory changes. In adipose tissue (FAT) cells, the most significant: activation of kinase inhibitor (Inhibitor of kappa B kinase — IKK), c-Jun N-terminal kinase (c-Jun N-terminal kinase —JNK), endoplasmic reticulum enzymes, protein kinase-C (PK-C), as well as oxidative stress — a violation of the relationship between reactive oxygen species and antioxidant protective factors [27]. Activation of IK, JNK, PK-C in the cytosol leads to the release of the nuclear transcription factor NF-kB (Nuclear factor kappa B), which migrates into the cell nucleus and stimulates the transcription of genes of numerous regulatory substances, including adipokines, TNF, IL, chemokines, inhibitors and activators of apoptosis, etc. The mechanisms initiating these reactions in adipocytes have not been definitively established. The idea of the leading role of cytokines secreted by activated proinflammatory macrophages of the gastrointestinal tract and, possibly, other substances dominates. Cytokines, primarily TNFa, induce a range of inflammatory shifts in adipocytes, which, in turn, causes their intracellular hyperproduction, including TNFa, creating a picture of a "vicious circle". This fact served as the basis for the idea that once initiated, VJT progresses without the presence of additional factors [28].

The main systemic consequences of FGM are the development of diseases such as atherosclerosis, type 2 diabetes mellitus (DM2), metabolic syndrome (MS), non-alcoholic steatohepatitis, arterial hypertension (AH). Each of these conditions can exacerbate the severity of COVID-19.

Special attention should be paid to the assessment of the components of immunity in fat cells and their physiological role [24]. The presence of innate immunity receptors (Toll—like receptors - TLRs), primarily TLR4, has been established in the membranes of fat cells. TLRs recognize the molecular components of bacteria, viruses, fungi and other pathogens and activate proinflammatory signaling pathways. The specific ligand of TLR4 is lipopolysaccharide (LPS) from the wall of gram-negative bacteria. In a healthy person, the source of LPS is microorganisms inhabiting the intestine. Activation of TLR4 stimulates intracellular kinases, which eventually ensures the translocation of the nuclear factor NF-kB into the cell nucleus, followed by stimulation of transcription of many pro-inflammatory genes encoding the synthesis of inflammatory regulatory substances, including cytokines, chemokines, adipokines. In particular, TLR4 stimulation of isolated adipocytes increases the secretion of IL-6, TNF-α, resistin, and reduces the level of adiponectin [29]. The combination of these reactions causes the development of insulin resistance (IR), not only in adipocytes, but also in hepatocytes and muscle cells. Activation of TLRs also enhances lipolysis. In studies on rodents, it was found that the presence of TLR4 is a necessary condition for the development of inflammation of adipose tissue due to its infiltration by macrophages. Consequently, the activation of TLRs causes a complex of changes in the VT characteristic of the VT [30].

Viral infections, in particular, coronavirus infection, enhance the effects of cytokines, generalizing nonspecific inflammation. Adipose tissue can act as a reservoir for a number of viruses, such as influenza, HIV and cytomegalovirus, and, according to recent data, it can also be activated with OVID-19. An unexpected feature of the coronavirus in acute respiratory failure is its ability to spread rapidly from the affected organ into the surrounding adipose tissue, affecting vital organs [31]. As a result, patients remain carriers and distributors of coronavirus for longer. This determines the peculiarities of the therapeutic approach to such patients, including longer isolation and inpatient treatment.

Another factor in the deterioration of the course of COVID-19 in patients with LV is a change in the activity of the enzyme dipeptidyl peptidase-4 (DPP-4). This enzyme is a type II transmembrane glycoprotein, which is produced in many tissues, including cells of the immune system. Currently, the functions of DPP-4 have not been sufficiently studied, but it is known that it participates in the degradation of various hormones and proteins [32], in particular, incretins. The cleavage of incretins (glucagon-like peptide 1 and (insulinotropic peptide) determines the important role of DPP-4 in the metabolism of insulin and glucose. In visceral LV, which is often combined with type 2 diabetes, an increase in the production of DPP-4 in the gastrointestinal tract leads to an increase in LVT, an increase in the degree of IR, a decrease in insulin secretion and metabolic disorders in the gastrointestinal tract itself [36], which, in turn, leads to the activation of catalytic enzymes and a decrease in the activity of immune mechanisms. It has also been established that one of the

components of the coronavirus, the so-called spike protein (HCoV-EMC), has an affinity for DPP-4 [33,34]. In vitro studies have shown that antibodies to DPP-4 are able to inhibit HCoV-EMC infection in bronchial epithelial cells and Huh7 cells [34] and interfere with the formation of an immune response. It has been established that MERS coronaviruses use the DPP-4 enzyme to enter the cell, while the SARS-CoV-2 virus uses ACE 2 to enter the cell. The problem of studying the mechanisms of coronavirus penetration into the cell and ways to inhibit them is promising for the development of COVID-19 treatment methods [35].

Currently, it is well known that LV, especially of a pronounced degree, is associated with a twofold risk of developing type 2 diabetes and a tenfold risk of cardiovascular death compared with people with normal body weight [36]. Thus, the severe course of COVID-19 is most often observed in people with concomitant diseases such as diabetes, healthy lifestyle, and cardiovascular pathology [36].

This is confirmed by observations that have demonstrated a high prevalence of OH in people with COVID-19, and a significant association of the severity of the disease with the presence and degree of OH. In particular, it was noted that a feature of patients with severe COVID-19 is the presence of polymorbidity, while LV is the second most common concomitant pathology (48.3%) after hypertension (49.7%) [37]. In the age group from 18 to 49 years, OJ was registered more often than chronic lung diseases and C. A similar pattern was also revealed in the age group of 50-64 years; and in the older age group (≥65 years), hypertension was most common.

A study by Chinese scientists involving 1,099 hospitalized and outpatient patients with COVID-19 (median age 47 years, most of them (58%) men) showed that the structure of comorbidity was more often determined by hypertension (14.9%), CT (7.4%) and coronary heart disease (2.5%) [38].

An observation by British researchers, which included almost 2 million people, demonstrated that severe LV is a risk of increased mortality in people with COVID-19 only in the presence of two or more comorbid conditions [39].

According to modern data, the combination of LV and CV in men is accompanied by an extremely severe course of it, requiring connection to artificial lung ventilation (ventilator) devices [47]. Thus, French studies demonstrate that the frequency of ventilator use in intensive care units for the treatment of patients with severe CVI is more than 7 times higher than that for people with a BMI>35 kg/m2 compared with patients with a BMI<25 kg/m2 [40]. Among 124 patients with OVID-19 at the French hospital (CHU Lille), 47.6% had LV, while 28.2% had a BMI exceeding 35 kg/m2. The prevalence of LV in the group of patients who required ventilation was 68.6%. At the same time, in all cases, the need for ventilation was due to a critical decrease in respiratory function with severe hypoxia. As the severity of LV increased, the number of patients requiring ventilation increased, reaching maximum values at a BMI of≥35 with a significant association with the male sex. An interesting fact is that the presented study did not reveal a relationship between the

severity of the infectious disease with age, the presence of diabetes, hypertension [41].

Currently, data have already been accumulated that indicate that cancer and related conditions (such as C, hypertension) are associated with a more severe course of COVID-19 and a fatal outcome [42, 43]. It is also known that the presence of CV and is associated with the risk of hyperglycemia, especially in the elderly over 60 years of age with diabetes [44].

Mechanisms that aggravate the course of COVID-19 and worsen the prognosis in patients with LV include impaired immune regulation, critical deficiency of cardiorespiratory reserve against the background of chronic cardiovascular diseases and chronic obstructive pulmonary disease (COPD) [45]. All this ultimately leads to multiple organ failure, which is the cause of death in this category of patients [46]. Obese people belong to the group with an increased risk of infection and an unfavorable prognosis of COVID-19 [47].

A direct link has been proven between the severe course of COVID-19 and the high frequency of disseminated intravascular coagulation syndrome (DIC syndrome), as well as venous thromboembolism. These complications are most often reported in patients with LV, which is an independent risk factor for thrombosis and thromboembolism [48].

Activation of ACE 2 expression against the background of CVI can also serve as one of the mechanisms of acute myocardial damage with the development of lightning myocarditis [49].

It should be noted that the abdominal type of obesity itself is associated with a deterioration in pulmonary ventilation, which significantly reduces blood oxygen saturation [50]. Pulmonary ventilation disorders and associated respiratory failure are often the cause of emergency hospitalization of patients with LV. It has also been proven that the majority of patients with severe acute respiratory failure have more severe manifestations of obstructive sleep apnea syndrome compared to people with normal body weight [50]. Thus, severe respiratory failure characteristic of patients with COVID-19 on the background of acute respiratory failure is a consequence of two mutually aggravating factors: the presence of viral pneumonia on the one hand and hypoventilation syndrome due to acute respiratory failure on the other.

The lessons of previous epidemics caused by coronaviruses demonstrate the development of acute coronary syndrome, arrhythmias, decompensation of heart failure, thromboembolic complications mainly due to a combination of a significant systemic inflammatory response and localized inflammation of the vascular wall. COVID-19 is no exception and worsens the clinical course of comorbid pathology in obesity, leading to the development of life-threatening complications. It should be noted that during epidemics, including COVID-19, most patients die more often from cardiovascular diseases [51].

Conclusion

Thus, at present, the problem of obesity against the background of the pandemic of a new coronavirus infection is of particular importance. On the one hand, the prevalence of OH among the population is steadily increasing, on the other hand, it has been proven that obese people are at risk of infection and severe COVID-19. This is due to the presence of high expression of angiotensin converting enzyme 2, the likelihood of developing a "cytokine storm", a chronic inflammatory process in adipose tissue, changes in the activity of dipeptidyl peptidase-4, which lead to impaired metabolism in adipose tissue and immune mechanisms of antiviral protection.

Patients with COVID-19 and obesity are more likely to require hospitalization in intensive care and intensive care units, and connection to artificial lung ventilation devices.

Currently, many features of the course of coronavirus infection against the background of obesity have been identified. These include: the presence of severe respiratory failure, a high risk of developing respiratory distress syndrome, thrombosis and thromboembolic complications, as well as worsening of the course of chronic cardiovascular diseases. All this eventually leads to the development of severe multiple organ failure, which is the cause of death in this category of patients.

In this situation, the issues of drug therapy, taking into account the mechanisms of virus penetration into the cell, the peculiarities of its pathophysiology and interaction with the human body, are of particular relevance.

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