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КОРОНАВИРУСНАЯ ИНФЕКЦИЯ У ПАЦИЕНТА С ОЖИРЕНИЕМ (ОБЗОР ЛИТЕРАТУРЫ)

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Coronavirus Infection an Obese Patient (Literature Review)

Резюме

В современном мире проблема ожирения на фоне пандемии новой коронавирусной инфекции приобрела особую опасность. С одной стороны, распространенность ожирения среди населения неуклонно растет, с другой — доказано, что лица с ожирением относятся к группе наиболее уязвимых в аспекте повышенного риска заражения и неблагоприятного прогноза. Это связано с наличием и особенностями развития различных патологических механизмов у данной категории больных. К ним относятся высокая экспрессия ангиотензинпревращающего фермента 2, высокая вероятность развития «цитокинового шторма», поддержание хронического воспалительного процесса в жировой ткани, изменение активности фермента дипептидилпептидазы-4, которые приводят к усугублению нарушения метаболизма в жировой ткани, а также нарушению иммунной протекции. Тяжесть состояния больных с ожирением, госпитализированных с COVID-19 (COronaVIrus Disease 2019), обусловлена наличием полиморбидности. Мировая врачебная практика в борьбе с пандемией COVID-19 показывает, что больные коронавирусной инфекцией на фоне ожирения чаще требуют госпитализации в отделения реанимации и интенсивной терапии и подключения к аппаратам искусственной вентиляции легких. В настоящее время продолжают изучаться особенности течения коронавирусной инфекции на фоне ожирения. К их числу относятся наличие тяжелой дыхательной недостаточности, высокий риск развития респираторного дистресс-синдрома, тромбозов и тромбоэмболических осложнений, а также ухудшение течения хронических сердечно-сосудистых заболеваний, что приводит к развитию полиорганной недостаточности и смерти. Разработка лекарственных препаратов учитывает механизмы проникновения вируса в клетку, особенности его патофизиологии и взаимодействия с организмом человека.

Ключевые слова: *ожирение, коронавирусная инфекция, ангиотензинпревращающий фермент, цитокиновый шторм, респираторный дистресс-синдром*

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Abstract

In the modern world the problem of obesity in combination with new coronavirus infection has acquired a special danger. On the one hand, the prevalence of obesity among the population is steadily increasing, on the other-it has been proven that obese people are among the most vulnerable in terms of increased risk of infection and a serious 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 a «cytokine storm» developing, maintenance of a chronic inflammatory process in adipose tissue, changes in the activity of Dipeptidyl peptidase-4 enzyme. All these processes lead to an aggravation of metabolic disorders in adipose tissue and violation of immune protection. The world medical practice in the fight against the COVID-19 pandemic shows that patients with coronavirus infection against the background of obesity more often need hospitalization in intensive care units and connection to artificial ventilation equipment. Currently, many features of the course of coronavirus infection against the background of obesity have been identified and 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. All this eventually leads to the development of severe multiple organ failure, which is often the cause of death in this category of patients.

Key words: *obesity, coronavirus infection, angiotensin converting enzyme, cytokine storm, respiratory distress syndrome*

Conflict of interests

The authors declare no conflict of interests

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ACE-2 — angiotensin-converting enzyme 2, AT — adipose tissue, ATI — adipose tissue inflammation, AH — arterial hypertension, ARDS — acute respiratory distress syndrome, BMI — body mass index, BP — blood pressure, CHD — coronary heart disease, CVI — coronavirus infection, DM — diabetes mellitus, DM 2 — type 2 diabetes mellitus, DPP-4 — dipeptidyl peptidase-4, IL — interleukin, IR — insulin resistance, MS — metabolic syndrome, MV — mechanical ventilation, OB — obesity, TNFα — tumor necrosis factor α

Introduction Coronavirus Pandemic in the Setting of Obesity Epidemic

The problem of obesity (OB) existed before the COVID-19 (COronaVIrus Disease 2019) pandemic. Today, obesity (OB) is regarded as one of the most critical diseases that lead to early disability and high mortality [1]. According to the World Health Organization (WHO, 2016), approximately 13% of the world's adult population is obese (11% of men and 15% of women) [2].

A study titled «Cardiovascular Epidemiology in Russian Federation» (ESSE-RF) revealed the prevalence of obesity among adults in 2014 of 29.7 ± 0.3% (30.8 ± 0.4% in women, 26.6 ± 0.5% in men) [3]. Today, about half (51.7% of women and 46.5% of men) of the Russian population has excess body weight and OB [4], while the number of patients with this disorder is constantly increasing [5]. An essential feature of our country is a significant increase in the prevalence of OB in men of working age; it is of great importance due to the increased cardiovascular risk.

Patients with OB proved to be most susceptible to the risk of various severe infectious diseases [2]. Examination of 268 patients hospitalized for influenza A (H1N1) in California demonstrated that 58% of them were diagnosed with OB; morbid obesity (body mass index (BMI) ≥40 kg/m^2) was associated with death. In another Mexican study, a higher risk of hospitalization in cases of OB was also confirmed — not only in the setting of influenza but also with other viral diseases such as parainfluenza, rhinovirus and metapneumovirus infections, as well as coronavirus disease [6].

The problem of OB combined with novel coronavirus infection (CVI) is of particular importance these days. The COVID-19 epidemic started in December 2019 in Wuhan (China) and spread rapidly across almost all countries. It was caused by the new SARS-CoV-2 coronavirus that induces severe acute respiratory syndrome (Severe Acute Respiratory Syndrome Coronavirus 2).

The current COVID-19 pandemic swept over Europe and North America, where the prevalence of OB is so high that it can be considered the «non-infectious epidemic of the 21st century» [7].

According to the World Health Organization, in May 2020, more than four million confirmed cases of COVID-19 were registered worldwide, including 280 thousand deaths. According to the official electronic information resource https://coronavirus-monitor.info, as of January 2021, the coronavirus disease (COVID-19) pandemic had affected 96 million patients and caused two million deaths. In Russia, as of that date, there were 3.6 million patients and 67 thousand fatal outcomes.

Pathophysiology of Severe Coronavirus Disease in Cases of Obesity

One of the reasons for the increased risk of CVI consequences with underlying OB is the activity of angiotensin-converting enzyme 2 (ACE2) [8, 9]. It was established that overweight triggers the expression of the parts of genes responsible for ACE-2 protein production [10, 11]. This protein is the «site of entry» for the SARS-CoV-2 virus into a cell. ACE-2 is involved in blood pressure (BP) regulation due to the inhibition of the activity of the renin-angiotensin system, vasodilation, increased natriuresis and suppression of the inflammatory process. ACE-2 is also a SARS-CoV-2 receptor that interacts with amino acid transporters and integrins [11]. Expression of ACE-2 occurs mainly in smooth muscle cells, endothelial cells, pancreatic acini, renal tubular epithelium, and adipocytes [12-14]. In adipose tissue, adipocytes themselves and other cells (stromal cells, endothelial cells, macrophages and lymphocytes) can be the targets for viruses [15]. Analysis of the risk of infection with various viruses in the population demonstrated a low prevalence of SARS-CoV-2 in cases of OB [16]. However, considering the high affinity of target cells, including adipocytes, for receptors, we can assume a hematogenous route of distribution in adipose tissue, which increases the risk of disease in this group of patients.

It is notabe that male individuals are characterized by higher ACE-2 expression. This feature determines the increased risk of COVID-19 due to the higher actual body fat percentage in cases of OB [17]. According to the literature, among 41 patients hospitalized for verified COVID-19 in China, 73% of cases were male patients [18]. Analysis of the gender ratio of patients in the USA demonstrated the same pattern, with males dominating (12.2%) among patients with severe coronavirus disease (16%).

Increased risk of severe COVID-19 consequences in individuals with OB is also determined by the higher possibility of a «cytokine storm». A cytokine storm is an uncontrolled and non-protective response of the body's immune system that affects healthy tissues. Today, the term «cytokine storm» has no generally accepted definition; it just means a hyperactive immune response characterized by excessive production of interferons, interleukins, chemokines, tumor necrosis factor, colony-stimulating factor and some other mediators that are part of the immune response required for effective counteraction of the causative agents of infectious diseases. This uncontrollable increase of the synthesis of pro-inflammatory mediators is also called hypercytokinemia and cytokine cascade [19, 21].

It was established that OB and metabolic syndrome are accompanied by the production of proinflammatory cytokines and increased acute-phase proteins, leading to chronic inflammation. Patients with OB have higher activity of nuclear transcription factor-kappa B (NF-κB) and intensive production of proinflammatory cytokines such as tumor necrosis factor α (TNFα), interleukin-1 (IL-1) and interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), plasminogen activator inhibitor (PAI-1); all these are factors actively synthesized by adipocytes in cases of OB [20]. OB is characterized by impaired congenital and acquired immunity, central and peripheral meta-inflammation (chronic systemic inflammation). Cellular hypoxia, mechanical stress of adipocytes, and excessive free fatty acids and lipopolysaccharides are the primary initiators of meta-inflammation [22, 23].

A cytokine storm involves a wide range of various clinical and laboratory abnormalities that are the features of a generalized systemic inflammatory response. In the respiratory tract, this can be manifested by severe pneumonitis, pulmonary edema, acute respiratory distress syndrome (ARDS), and severe hypoxemia. Severe cytokine storms may cause renal and hepatic failure, cholestasis, and cardiomyopathy. The combination of renal failure, death of endothelial cells and hypoalbuminemia can lead to a systemic increase in capillary permeability and edematous syndrome. Neurological toxic effects of a cytokine storm are often delayed and manifest as encephalopathy of different severity [21, 24].

SARS-CoV-2 leads to the activation of monocytes, macrophages and dendritic cells and the release of IL-6, which activates cis-acting signals and pleiotropic effects of the immune system. A randomized multicenter study demonstrated that IL-6 is a strong independent predictor of death in cases of COVID-19. By its nature, adipose tissue is the main source of IL-6 and its receptor, IL-6R [25]. The ability of coronavirus to "cling" to IL-6 and its receptors was established; it ensures cascade transmission of viral signals and effects.

A large amount of adipose tissue is by itself a constant source of pro-inflammatory cytokines synthesized both by adipocytes themselves and by macrophages migrating into adipose tissue, leading, as already mentioned, to the development and sustenance of a chronic slow inflammatory process in the body. In turn, pathological secretion of adipokines in adipose tissue (IL-1, IL-6, TNFα) in combination with increased C-reactive protein, leptin-to-adiponectin ratio and decreased protective factors (adiponectin, anti-inflammatory cytokine IL-10) are accompanied by a deteriorated immune response and adverse effects for all organs and tissues, including pulmonary parenchyma and bronchi [26, 27]. It was established that the increase in pro-inflammatory biomarkers

is in direct proportion to the severity of OB. Disorders of endocrine function in abdominal OB with the accumulation of visceral fat, including pericardial and perivascular fat, create conditions for the development of the inflammatory process that plays a significant role in comorbid pathology (see Fig. 1).

Local and systemic pathological changes caused by adipose tissue inflammation (ATI) are primarily due to intracellular inflammatory changes. The most significant processes in adipose tissue (AT) cells are: activation of kinase inhibitor (Inhibitor of kappa B kinase — IKK), c-Jun N-terminal kinase (JNK), endoplasmic reticulum enzymes, protein kinase-C (PK-C), as well as oxidative stress — impaired relationship between reactive oxygen species and antioxidant protective factors [27]. Activation of IKK, JNK, PK-C in cytosol leads to the release of nuclear transcription factor NF-κB (nuclear factor kappa B) that migrates to the cell nucleus and stimulates the transcription of genes of numerous regulatory substances, including adipokines, TNFα, IL, chemokines, inhibitors and activators of apoptosis, etc. Mechanisms that induce these reactions in adipocytes are not yet fully established. The prevailing idea suggests the leading role of cytokines secreted by activated pro-inflammatory macrophages in AT and, possibly, by other substances. Cytokines, primarily TNFα, induce a number of inflammatory changes in adipocytes, which, in turn, causes their intracellular hyperproduction, including TNFα, thus developing a kind of a «vicious circle». This fact was the basis for the idea that once initiated, ATI progresses without the help of additional factors [28].

The main systemic consequence of ATI is the development of the following diseases: atherosclerosis, type 2 diabetes mellitus (DM 2), metabolic syndrome (MS), non-alcoholic steatohepatitis, and arterial hypertension (AH). Each of these conditions may exacerbate the severity of COVID-19.

Special attention should be paid to the assessment of the immunity components in fat cells and their physiological role [24]. Innate immunity receptors, toll-like receptors (TLRs), primarily TLR4, were found in fatty cell membranes. TLRs recognize the molecular components of bacteria, viruses, fungi and other pathogens and activate pro-inflammatory signaling pathways. Lipopolysaccharide (LPS) from the wall of gram-negative bacteria is a specific TLR4 ligand. The source of LPS in healthy individuals is intestinal microorganisms. Activation of TLR4 stimulates intracellular kinases, which ultimately translocates the NF-κB nuclear factor into the cell nucleus, followed by stimulation of the transcription of many pro-inflammatory genes that encode the synthesis of inflammatory regulatory substances including cytokines, chemokines, adipokines. In particular, the

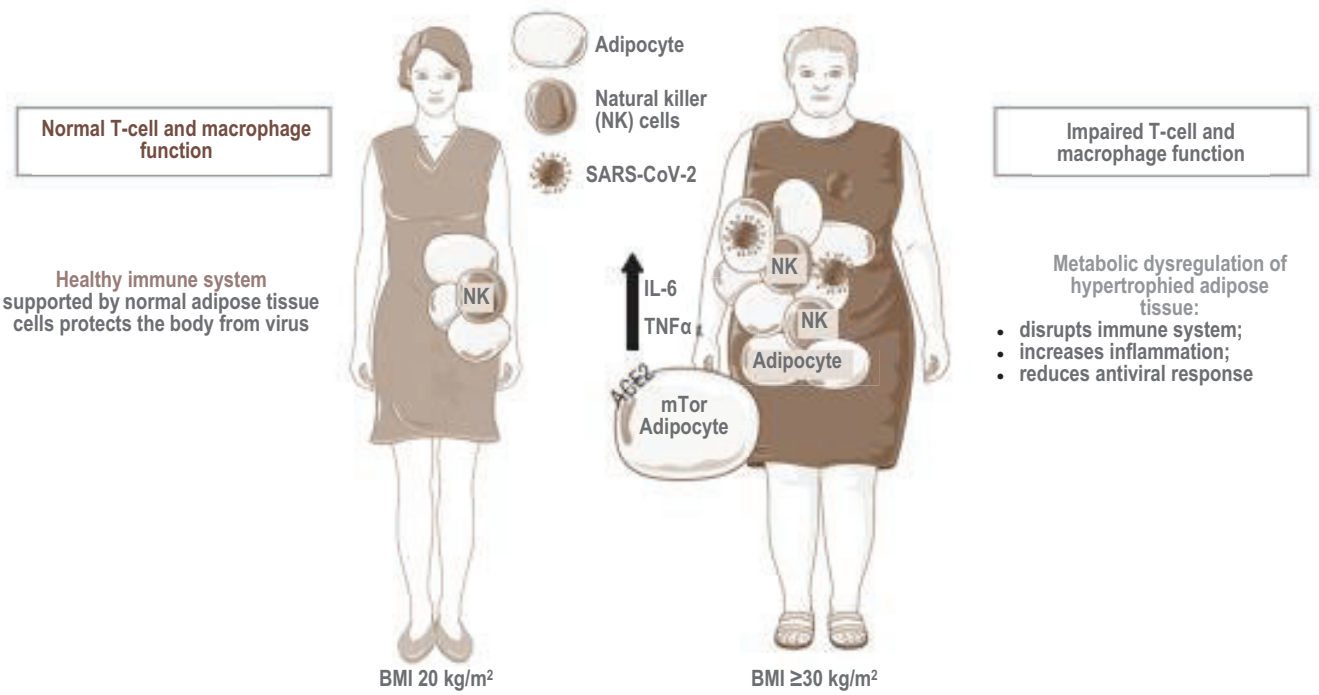

Figure 1. *Features of the pathogenesis of the severe course of coronavirus infection in obesity. Th e activity of immune cells and the secretion of proinfl ammatory cytokines increase in adipose tissue — this leads to hyperinfl ammation and the development of a «cytokine storm» [18]*

stimulation of TLR4 in isolated adipocytes increases the secretion of IL-6, TNFα, resistin and decreases adiponectin level [29]. The combination of these reactions causes the development of insulin resistance (IR), not only in adipocytes but also in hepatocytes and muscle cells. The activation of TLRs also increases lipolysis. Studies on rodents revealed that TLR4 is a necessary condition for the development of adipose tissue inflammation due to its infiltration by macrophages. Consequently, the activation of TLRs in AT causes a complex of changes typical for ATI [30].

Viral infections, particularly coronavirus infection, enhance the effect of cytokines, generalizing non-specific inflammation. Adipose tissue can act as a reservoir for a number of viruses, such as influenza, HIV and cytomegalovirus; according to recent data, COVID-19 can also be activated in it. An unexpected feature of coronavirus in cases of OB is its ability to quickly spread from the affected organ to the surrounding fatty tissue, affecting vital organs [31]. As a result, patients carry and spread coronavirus longer. This determines the specific features of the therapeutic approach to such patients, among other things — longer isolation and inpatient treatment.

Another factor of deterioration in COVID-19 patients with OB is the change in the activity of the dipeptidyl peptidase-4 (DPP-4) enzyme. This enzyme is a type II transmembrane glycoprotein produced in many tissues, including cells of the immune system. Functions of DPP-4 are not yet well understood, but we know that it is involved in the degradation of various hormones and proteins [32], particularly 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 patients with visceral OB, which is often coupled with type 2 DM, increased production of DPP-4 in AT leads to increased ATI, increased IR, decreased insulin secretion, and metabolic impairment in AT itself [36], which, in turn, results in the activation of catalytic enzymes and decreased activity of immune mechanisms. It was also established that one of the components of coronavirus, the so-called spike protein (hCOV-EMC), has an affinity for DPP-4 [33,34]. In vitro studies revealed that antibodies to DPP-4 are able to inhibit hCOV-EMC infection in bronchial epithelial cells and Huh-7 cells [34] and interfere with the development of immune response. It was found that MERS-coronaviruses use the DPP-4 enzyme to enter cells while SARS-CoV-2 virus uses ACE-2 for the same purpose. The study of the mechanisms of how coronavirus enters cells and ways of inhibiting these mechanisms is promising for the development of COVID-19 treatment methods [35].

Study Data on the Course of Coronavirus Disease in Obesity

It is well known that OB, particularly severe OB, is associated with a twofold risk of type 2 DM and a tenfold risk of cardiovascular death compared with individuals with normal body weight [36]. Therefore, a severe course of COVID-19 is most often observed in patients with comorbidities such as DM, OB, and cardiovascular diseases [36].

This was confirmed by observations demonstrating a high prevalence of OB in individuals with COVID-19 and a significant association of disease severity with the presence and grade of OB. In particular, a specific feature of patients with severe COVID-19 is polymorbidity. OB is the second most common comorbidity (48.3%) after AH (49.7%) [37]. In the 18-49 age group, OB was observed more often than chronic lung diseases and DM. A similar pattern was also determined in the 50-64 age group and in elderly patients (≥65), AH was the most common comorbidity.

A study performed by Chinese scientists, which involved 1,099 hospitalized patients and outpatients with COVID-19 (median age 47 years, majority (58%) — male subjects), demonstrated that AH (14.9%), DM (7.4%) and CHD (2.5%) were the most common comorbidities [38].

The observation carried out by British researchers, which included almost two million individuals, revealed that severe OB was the risk of increased mortality in individuals with COVID-19 only if they had two or more comorbid conditions [39].

According to current data, OB coupled with CVI in men leads to an extremely severe course of the disease, which requires mechanical ventilation (MV) [47]. French studies have shown that the frequency of mechanical ventilation used in intensive care units for the management of severe CVI is more than seven times higher for patients with BMI >35 kg/m^2 compared with patients with BMI <25 kg/m^2 [40]. Among 124 COVID-19 patients at one French hospital (CHU Lille), 47.6% were obese, while 28.2% had a BMI higher than 35 kg/m^2. The prevalence of OB in the group of patients who required mechanical ventilation was 68.6%. In all cases, the need for mechanical ventilation was due to a critical decrease in respiratory function with severe hypoxia. The number of patients requiring mechanical ventilation increased with the increased severity of OB, reaching maximum values at BMI ≥35 with significant association with the male gender. Interestingly, there was no link between the severity of the infectious disease with age, DM, or AH [41] in this study.

Today, we have accumulated evidence about the association of OB and its related conditions (such as DM, AH)

with a more severe course of COVID-19 and death [42, 43]. It is also known that CVI is associated with the risk of hyperglycemia, especially in elderly patients aged 60+ with DM [44].

Mechanisms that aggravate the course of COVID-19 and worsen the prognosis in patients with OB include impaired immune regulation, critical deficiency of cardiac and respiratory reserve with underlying chronic cardiovascular diseases and chronic obstructive pulmonary disease (COPD) [45]. As a result, all these factors lead to multiple organ failure, which is the cause of death in this category of patients [46]. Obese individuals are at increased risk of COVID-19 infection and poor prognosis [47].

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

Activation of ACE-2 expression in cases of CVI can also be one of the mechanisms of acute myocardial damage with the development of fulminant myocarditis [49].

It should be noted that abdominal OB itself is associated with worsened pulmonary ventilation, which significantly reduces blood oxygen saturation [50]. Pulmonary ventilation disorders and associated respiratory failure are the common cause of emergency hospitalization of obese patients. It was also proved that most patients with severe OB have more severe manifestations of obstructive sleep apnea compared with individuals with normal body weight [50]. Therefore, severe respiratory failure, which is typical for patients with COVID-19 and underlying OB, is a consequence of two mutually aggravating factors: viral pneumonia on the one hand and hypoventilation syndrome due to OB on the other hand.

Lessons from past coronavirus epidemics demonstrate the development of acute coronary syndrome, arrhythmias, decompensation of heart failure, thromboembolic complications primarily due to the combination of significant systemic inflammatory response and localized inflammation of the vascular wall. COVID-19 is no exception: it worsens the clinical course of comorbidities in cases of obesity, leading to the development of life-threatening complications. It should be noted that during epidemics, including COVID-19, most patients die from cardiovascular diseases [51].

Conclusion

Therefore, the current problem of obesity amid the coronavirus pandemic is of particular importance. On the one hand, the prevalence of OB among the population is steadily increasing. On the other hand, it was proven that obese individuals are at risk of infection and severe COVID-19. This is due to the high expression of angiotensin-converting enzyme 2, possible development of a «cytokine storm», chronic inflammatory process in adipose tissue, and changes in the activity of dipeptidyl peptidase-4; all these factors lead to impaired metabolism in adipose tissue and impaired immune mechanisms of antiviral defense.

Obese COVID-19 patients are more often hospitalized in the intensive care unit and more often require mechanical ventilation.

Many typical features of the course of coronavirus disease in cases of obesity have been identified. These include: severe respiratory failure, high risk of respiratory distress syndrome, thrombosis and thromboembolic complications, as well as worsening of chronic cardiovascular diseases. All these factors ultimately lead to severe multiple organ failure, which is the cause of death in this category of patients.

The issues of drug treatment, taking into account mechanisms of virus entry into cells, especially its pathophysiology and interaction with the human body, are of particular relevance in this situation.

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