EDITORIAL

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CLINICAL FEATURES, TREATMENT AND REHABILITATION OF NEW CORONAVIRUS INFECTION IN PATIENTS WITH METABOLIC SYNDROME

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This review examines the main aspects of the course of a new coronavirus infection in patients with metabolic syndrome, provides up-to-date statistics on morbidity and mortality. Abdominal obesity, insulin resistance, arterial hypertension and dyslipidemia, which form the metabolic syndrome, are independent factors of a severe course of infection with a high risk of developing SARS, various complications, mainly the development of acute respiratory distress syndrome, extrapulmonary systemic inflammation and, finally, death. During the period of anti-epidemic measures, children turn out to be the most vulnerable in terms of losing the rational, healthy stereotypes of nutrition, regulation of "screen time", responsible planning of study time and leisure, regular and intense physical activity. It requires increased attention of doctors, teachers and rehabilitation specialists to the problem maintaining the commitment of children and parents to a healthy lifestyle. Based on the formed concept of the presence of common links in the pathogenesis of the development of metabolic disorders and the infectious process, the authors identified the most significant issues of therapy and rehabilitation of this category of patients. Taking into account the need of patients for psychological adaptation of the past illness and increasing their resistance to stressful situations, within the framework of providing a personalized approach to the management of patients, may require timely diagnosis of anxiety-depressive disorders with the appointment of appropriate therapeutic measures.

Keywords: metabolic syndrome; obesity; arterial hypertension; diabetes mellitus; dyslipidemia; novel coronavirus infection; COVID-19; pathogenesis; treatment; rehabilitation.

ОСОБЕННОСТИ ТЕЧЕНИЯ, ЛЕЧЕНИЯ И РЕАБИЛИТАЦИИ НОВОЙ КОРОНАВИРУСНОЙ ИНФЕКЦИИ У ПАЦИЕНТОВ С МЕТАБОЛИЧЕСКИМ СИНДРОМОМ

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В обзорной статье рассматриваются основные аспекты течения новой коронавирусной инфекции у пациентов с метаболическим синдромом, приводятся актуальные статистические данные о заболеваемости и смертности. Абдоминальное ожирение, инсулинорезистентность, артериальная гипертензия и дислипидемия, формирующие метаболический синдром, являются независимыми факторами тяжелого течения инфекции с высоким риском развития атипичной пневмонии, разнообразных осложнений, преимущественно, развития острого респираторного дистресс-синдрома, внелегочного системного воспаления и, наконец, наступлением летального исхода. В период противоэпидемических мероприятий дети оказываются наиболее уязвимыми в плане утраты важнейших рациональных, здоровых стереотипов питания, регламентирования «экранного» времени, ответственного планирования

учебного времени и досуга, регулярных и интенсивных физических нагрузок, что требует повышенного внимания врачей, педагогов и специалистов по реабилитации к проблеме сохранения приверженности детей и родителей здоровому образу жизни. Основываясь на сформированном представлении о наличии общих звеньев в патогенезе развития метаболических нарушений и инфекционного процесса, авторы выделили наиболее значимые вопросы терапии и реабилитации данной категории больных. Учитывая потребность пациентов в психологической адаптации перенесенной болезни и повышении их устойчивости к стрессовым ситуациям, в рамках обеспечения персонифицированного подхода в ведении больных может потребоваться своевременная диагностика тревожно-депрессивных расстройств с назначением соответствующих лечебных мероприятий.

Ключевые слова: метаболический синдром; ожирение; артериальная гипертензия; сахарный диабет; дислипидемия; новая коронавирусная инфекция; COVID-19; патогенез; лечение; реабилитация.

METABOLIC SYNDROME AND COVID-19

According to data compiled by The Center for Systems Science and Engineering, based at Johns Hopkins University, as of July 2, 2021, more than 182 million cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection were globally registered, and nearly 4 million people had lethal outcomes [24]. The global spread of the coronavirus disease 2019 (COVID-19), new coronavirus infection, predetermined the offset in the direction of research activities toward studying the conditions for the occurrence, ways, and mechanisms of the disease spread to determine and implement the most effective preventive and anti-epidemic measures. In this pandemic, in addition to the currently identified biomedical, sociopsychological, and economic problems, the predicted stagnation of the epidemiological transition due to a change in the structure of mortality in the global population is no less important, which highly necessitates the revision of prevailing ideas about the examined pathological conditions. In the meta-analyses conducted to assess the characteristics of the clinical manifestation and outcomes of coronavirus infection among patients with comorbid pathology, the most unfavorable prognostic course of the disease was noted in persons with metabolic disorders, which are characterized by common pathogenetic mechanisms, such as metabolic syndrome (MS).

Obesity is a fundamental factor that triggers a cascade of metabolic disorders, and its pathogenesis is closely related to insulin resistance (IR). Based on available statistics, obesity is diagnosed in, on average, 20%–30% of the population of economically developed countries. According to the emerging tendency, by 2025, body mass index (BMI) will exceed 30.0 kg/m^2 in 1 of 5 people [57]. In 2019, approximately 352 million people aged 20–64 years and 1 of 5 (approximately 111 million) people aged >65 years had an established diagnosis of type 2 diabetes mellitus (DM). By 2030, these indicators are estimated to affect 417 and 195 million people, respectively [43].

The analysis of possible factors in 2020, associated with the risk of coronavirus infection, conducted by Fan et al. [28] at the Veterans Health Administration (Washington), was one of the first reports that formed the basis of the hypothesis that obesity is associated with a more severe course of COVID-19, and 10.5% of 10,131 patients with a positive polymerase chain reaction test for the presence of RNA virus in nucleic acid preparations were overweight [28]. Nevertheless, data obtained could not be extrapolated completely to the US population due to the aspects of the sample formation. A cohort study of nearly 400 thousand cases of SARS-CoV-2 infection in the UK, which assessed the conditions that influenced the need for hospitalization, had provided more information. Obesity and low physical activity were identified among major factors that presumably cause more pronounced disease symptoms with a high risk of complications that consequently require inpatient treatment. The relative risks (RRs) calculated based on the data obtained for these indicators were 1.32 (95% confidence interval [CI] 1.10–1.58) and 2.05 (95% CI 1.68–2.49), respectively [33]. In a study of 9905 patients seeking medical care in outpatient and inpatient facilities in Sweden, a threefold increase in the risk of a complicated COVID-19 course was found among patients with obesity [7]. The results of the Spanish cohort study, which included 2226 cases, indicated a high probability of lethal outcomes (in approximately 50% of cases) in representatives of the described category of patients [5].

The finding that excess body weight is an aggravating factor of the course of COVID-19 was also evidenced by data presented by researchers from several countries. According to Rottoli et al. (Italy) [64] and Steinberg et al. [78] (USA), the incidence of indications for inpatient treatment was two times higher in patients with obesity. Moreover, the probability of hospitalization in the resuscitation and intensive care unit (ICU), need for artificial pulmonary ventilation (APV) device,

and lethal outcomes of serious adverse events in such patients were 5–6 times higher [64].

Results of the statistical analysis of data from New Yorkers aged <60 years diagnosed with COVID-19, published by Petrilli et al. [59], revealed that those with BMI of 30–34.9 and >35 kg/m^2 had 1.8 and 3.6 times higher probability, respectively, of being hospitalized in the ICU. In the study by Simonnet et al. (France) [74], the calculated odds ratio for the APV use was 7.36 (95% CI 1.63–33.14) if the patient had grade II obesity (BMI >35 kg/m^2).

An important aspect revealed during a detailed consideration of this problem was an increased probability of severe COVID-19 and lethal outcome not only in patients with obesity but also in those with BMI >25 kg/m^2. A comparative analysis performed by Cai et al. [18] showed an increase in the probability of severe COVID-19 by 1.84 times (95% CI 0.99–3.43) in patients who were overweight and by 3.40 times in those with BMI >30 kg/m^2 (95% CI 1.40–2.86). An analysis of information about the disease course on 8.29 million patients in the UK, provided by general practitioners, showed that an overweight status increased the probability of a severe disease that requires intensive care by 67% and by nearly 3 times in patients with BMI >30 kg/m^2 [37].

At the beginning of 2021, based on the information collected from about a hundred studies (i.e., 40 systematic reviews and >20 meta-analyses) covering the populations of China, USA, and several European countries, the assumption of the effect of obesity on the severity of COVID-19, probability of ICU hospitalization, and need for APV was not only finally confirmed, but a global assessment of the dependence of mortality rates (per 100 thousand populations) on adult people who were overweight was performed. Correlation analysis of data reported by more than 160 countries revealed a noticeable direct relationship between these variables and a correlation coefficient r of 0.547 ($p < 0.001$) in countries where the proportion of the population with BMI >25 kg/m^2 was <50%. To extrapolate the data to other countries, a linear transformation was performed; as a result, the relationship found became closer ($r = 0.703$). Based on this, an increase in the number of people who were overweight of up to 50% in the working-age population was the threshold value at which the weighted average mortality rate increased from 4.5 to 66.8 cases per 100 thousand people.

The economic well-being of countries does not explain this tendency, as evidenced by the calculations of the World Obesity Federation, as in a comparative analysis of three representative groups, which, depending on the indicators of gross domestic product per capita and parity purchasing power, were expressed in US dollars, were distributed among 157 countries. Moreover, the relationship between the prevalence of obesity and the frequency of lethal outcomes from COVID-19 was registered in all groups [23].

A similar pattern was noted when collecting data on the course of COVID-19 in patients with IR. The results of a retrospective study of 451 patients with DM or newly diagnosed hyperglycemia indicated that an uncontrolled increase in blood glucose levels was associated with prolonged hospital stay and the risk of lethal outcome. However, two circumstances limited the use of the data, namely, during the study, the probability of uncontrolled glycemia due to COVID-19 was not considered, and a more detailed comparative analysis was not performed to determine type 1 and type 2 DM [15]. Another retrospective study presented the trends described, as the in-hospital mortality rate was lower in patients with well-controlled blood glucose concentrations (from 3.9 to 10.0 mmol/L) than in those with blood glucose levels >10.0 mmol/l, and the adjusted hazard ratio (HR) was 0.14 (95% CI 0.04–0.60) [92].

Furthermore, some published data refuted the assumption that the level of glycated hemoglobin (HbA1c) is associated with the probability of an adverse disease outcome in patients with type 2 DM, and the presence of which affected the severity of COVID-19 pneumonia [19]. A meta-analysis of 30 studies with a total of 6452 patients showed that in combination with age and presence of arterial hypertension (AH), type 2 DM increases the risk of severe disease by 2.45 times (95% CI 1.79–3.35) and lethal outcome by 2.12 times (95% CI 1.44–3.11) [41].

By contrast, the major population-based OpenSAFELY study, which pooled the information on primary health care for more than 17.2 million patients with COVID-19 with subsequent registration, showed that any type of DM is an independent risk factor of lethal outcomes, as the adjusted HRs were 1.95 (1.87–2.07) for patients with HbA1c >7.5% and 1.31 (95% CI 1.24–1.37) for those with HbA1c <58 mmol/mol [85].

In a cohort study, the risk of lethal outcomes in patients with type 2 DM as a result of acute respiratory distress syndrome or other complications was significantly higher in patients with HbA1c >7.6% and increased in direct proportion

to the growth of this indicator. For example, with HbA1c of 7.6%–8.9%, the HR coefficient was 1.22 (95% CI 1.15–1.30), while with HbA1c of 9.0%–9.9%, it increased up to 1.36 (95% CI 1.24–1.50). An important aspect was also the exposed inverse relationship between HbA1c values and mortality rate after reaching a threshold value of <48 mmol/mol (6.5%). Moreover, the risk ratio was significantly higher in young and middle-aged patients with type 2 DM than in patients aged >70 years, whereas in patients with type 1 DM, no such association with age was noted [39, 78].

Chinese studies have also found that diabetes can be regarded with a high degree of probability as one of the determinants of COVID-19 with severe clinical manifestations, atypical pneumonia, high risk of complications, and, consequently, lethal outcomes [31, 50, 86, 89], whereas a newly diagnosed hyperglycemia was a more unfavorable prognostic factor than a long history of DM [15, 75, 77].

AH and lipid metabolism disorders are equally significant in the aggravation of prognosis in patients with COVID-19 [44]. The aggravated course of COVID-19 in patients with AH was the most common comorbid pathology, as evidenced by the results of an analysis of 5700 patients hospitalized for COVID-19 in New York, and56.6% of these patients had elevated blood pressure (BP) values or an established AH. Obesity was a rarer comorbid pathology, which accounted for 41.7% of cases, and DM was revealed in 33.8% of the patients examined [61].

Similar data are presented in a retrospective study where AH was registered in 49% of patients with confirmed COVID-19 [29], similar to 50% of the deceased patients with AH who used APV and were in the ICU, according to Xie et al. [87]. A comparative analysis of the frequency of ICU hospitalization showed the predominance of AH as the most common comorbid pathology in this cohort [17, 81]. In the previously mentioned OpenSAFELY study, analysis of the change in the risk of lethal outcomes in patients with hypertension, taking into account the patient's age, revealed higher mortality in patients aged <70 years, whereas the concomitant effect of factors such as DM and obesity contributed to a decrease in the HR coefficient to 0.97 (95% CI 0.92–1.01) [85]. In some way, the association of AH with severe COVID-19 could be due to age or a severe pathological condition, which caused an increase in BP; therefore, it was not possible to regard AH as an independent predictor of indications of intensive treatment and increased risk of lethal outcomes.

Dyslipidemia is also associated with severe COVID-19; according to a meta-analysis of nine studies with 3663 cases, lipid metabolism disorders are associated with a nearly two-fold increase in the RR of an adverse outcome (1.39; 95% CI 1.02–1.88), being dependent on predictors such as age, male sex, and AH [11].

One of the arguments for the significance of dyslipidemia is based on the results of an assessment of 5279 patients with COVID-19 (NY, USA). Among them, patients with increased lipoprotein concentrations in the blood needed inpatient treatment more often (26% of all hospitalized patients), while the proportion of patients with hyperlipidemia was 11% of all mild COVID-19 cases. Among hospitalized cases, a similar pattern was noted, that is, the number of people with high blood lipid levels, discharged from the hospital and transferred to the ICU, was 24% compared with 27%, respectively [59].

A detailed examination of each cholesterol fraction separately revealed certain trends, that is, low concentrations of high-density lipoproteins (HDL) and high levels of triglycerides (TG) in the patient's blood, according to Masana et al. [53], can be considered a marker of the severity of the inflammation process and consequently a severe disease course. On the contrary, a 10 mg/dL increase in serum HDL or apolipoprotein A1 is associated with an approximately 10% reduction in the risk of COVID-19 [53]. According to various sources, the concentrations of low-density lipoproteins (LDL) in the blood before infection were significantly higher. Thus, in a retrospective analysis by Fan et al. [27], the level of LDL decreased to an average of 2.5 mmol/L with disease progression and returned within the range of reference values by recovery or irreversibly decreased to an average of 1.1 mmol/L until the lethal outcome. The results of the study of predictors of 30-day mortality, which included 654 cases, indicated relatively lower blood levels of total cholesterol and LDL of the deceased throughout the disease course. The correlation and multivariate analysis showed strong feedback with inflammation markers and a direct relationship with the lymphocyte count and ratio for lethal outcomes within 30 days after hospitalization, equal to 1.94 (95% CI 1.14–3.31), with a decrease in the LDL concentration in the blood to ≤69 mg/dl. Since such a course persisted for the first 7 days, LDL levels during this period could be regarded as a predictor of the further disease course [10].

Wang et al. [82] reported that the levels of total cholesterol, HDL, LDL, and TG in the blood of

patients with confirmed COVID-19 were significantly lower than those in the comparison group, namely, an average of 3.76 versus 4.65 mmol/L ($p = 0.031$), 0.78 versus 1.37 mmol/L ($p < 0.001$), 2.63 versus 2.83 mmol/L ($p < 0.001$), and 1.08 versus 1.21 mmol/L ($p < 0.001$), respectively. Moreover, lower blood concentrations of lipoproteins were recorded in patients with a complicated disease course [82].

Hu et al. [40] in a retrospective study of 597 patients found that HDL levels begin to decrease only in extremely severe infection, and similar results were obtained in another study [83]. In addition, during primary infection, the concentration of HDL was lower than in patients with secondary infection; thus, a hypothesis was proposed about the involvement of HDL in the cellular regulation of immune response.

Lipoproteins were suggested to affect SARS-CoV-2 replication, internalization, and activation of the immune system; therefore, a change in their blood level can be used in the indirect assessment of treatment efficiency [63]. The latter assumption can be supported by the evidence that when comparing the blood concentration of lipoproteins of patients at the time of hospitalization and 3–6 months after discharge, there was a tendency toward normalization of lipid metabolism, which corresponded to the radiological signs of partial resolution of changes in the lungs [12, 46]. Thus, each component of MS can be considered an independent factor in severe disease with a high risk of atypical pneumonia, various complications, and lethal outcome.

RELATIONSHIP MECHANISMS

COVID-19 can be roughly considered a process consisting of four phases, and phase 1 involves the primary manifestation of symptoms. The most common clinical manifestations at this phase are general weakness, dry cough, and fever. Depending on the conditions, phase 1 can proceed to phase 4 (period of recovery and restoration) and phase 2 (development of an inflammatory process in the lungs and pneumonia). In accordance with the absence or presence of a pneumonia-associated hypoxic condition, phase 2 is distinguished into 2a and 2b. At the onset of phase 2b, the patient should be hospitalized. This phase can be replaced by phase 3 or immediately by a period of convalescence bypassing it. The development of respiratory distress syndrome, a syndrome of extrapulmonary systemic inflammation, which is often accompanied by shock, angioparesis, respiratory failure, cardiopulmonary collapse, myocarditis, and acute kidney injury, characterizes phase 3 of the pathological process. It appears to be the most prognostically unfavorable variant of the disease course, associated with high risks of lethal outcomes. Based on the foregoing, MS is one of the most significant conditions contributing to the onset of phase 3 [73]. Based on currently available information on the pathogenesis of COVID-19, several mechanisms can be proposed to explain the described aspects of the disease course in patients with MS.

First, the pathogenetic justification for the formation of such dependence is an impairment of the para- and autocrine functions of adipose tissues due to a change in its structure and predominance of the visceral component. This is manifested as hypertrophy of adipocytes, which are actively involved in the production of tumor necrosis factor-α (TNF-α), leptin, monocyte chemoattractant protein 1 (MPC-1), C-reactive protein, interleukin-6 (IL-6), and IL-8. Hypoxia associated with a decrease in the vascularization of adipose tissues causes ischemic necrosis and apoptosis of hypertrophied adipocytes, which contributes to increased tissue infiltration by macrophages of the pro-inflammatory phenotype (M1), which in turn contribute to the production of IL-1β, IL-6, IL-17, IL-23, and TNF-α. In addition to macrophages, structures formed around dead adipocytes, including $CD8^+$ T-lymphocytes and B-lymphocytes. Consequently, the amount of pro-inflammatory mediators and class G immunoglobulin also increases. The active involvement of memory T-lymphocytes in adipose tissue and a decrease in the proliferation of regulatory T-cells producing anti-inflammatory IL-10 result in the depletion of their population, which limits the ability of the immune system to fight a viral infection, mainly due to the weakening of the interferon response [6, 21, 35, 49]. Moreover, remodeling of adipose tissue leads to a decrease in the concentration of adiponectin, which has anti-inflammatory, anti-atherogenic, and insulin-sensitizing effects, and adipocytes of the subcutaneous adipose tissues are mainly responsible for its expression [58, 88]. The imbalance toward the predominance of pro-inflammatory cytokines results in oxidative stress in adipose tissue and, consequently, chronic low-grade systemic inflammation [51, 52].

In summary, abdominal obesity contributes substantially to secondary infectious agents and a high probability of mixed infection with a dysfunctional immune response, which explains the high incidence of COVID-19 in this category of patients.

Moreover, the active production of pro-inflammatory cytokines acts as a substrate for the development of a multisystem inflammatory syndrome (so-called cytokine storm), which contributes to an increase in vascular permeability and impregnation of the lung tissues with neutrophils caused by the infiltration of these cells into the lungs following SARS-CoV-2 infection. The resulting neutrophil extracellular traps and products of cellular apoptosis trigger the recognition of viral patterns by innate immunity receptors, exacerbating the severity of the cytokine storm. This disrupts the function of intercellular contact proteins that form dense junction zones in the epithelium of the respiratory tract and makes the epithelium vulnerable, which contributes to the development of severe respiratory failure and respiratory distress syndrome, affecting significantly the prognosis [67].

Obesity plays a significant role in the formation of hyperglycemia and hyperinsulinemia, which determine the development of IR. An increase in TG level in visceral fat is associated with the slowing of the translocation in muscle cells of glucose transporters (GLUT-4) in case of physical inactivity and malnutrition and is a key factor that triggers the restructuring of membrane phospholipids. Consequently, at the genetic level, the mechanisms for conducting the insulin signal into the cell and an increase in the amount of lipids in the mitochondria of muscle fibers are impaired. The latter inhibits glycolysis by displacing the substrate in the Randle cycle, preventing the utilization of glucose by myocytes [9, 13].

In the range of the multiple effects of TNF-α, which blood concentration is increased in patients with obesity, slowing the expression of glucose substrate phosphorylation by inhibiting the insulin receptor tyrosine kinase and the production of GLUT-4 in muscle and adipose tissues also create conditions for hyperglycemia.

Non-esterified (free) fatty acids, produced through active lipid breakdown in visceral adipose tissue adipocytes, accumulate in the liver and negatively affect the ability of hepatocytes to extract insulin. Thus, the decreased sensitivity of hepatocytes to it progresses, which ensures the development of hyperinsulinemia. This state is prolonged by leptin, which stimulates simultaneously the production of insulin and inhibits its utilization, restricting the gluconeogenesis rate and slowing down glycolysis by inhibiting phosphofructokinase. One of the properties of insulin is the simultaneous stimulation of leptin mRNA expression, which starts a closed cycle.

In the case of hyperinsulinemia, the number of active insulin receptors steadily decreases, fixing the mechanism of IR formation. The processes of glucose utilization by peripheral tissues slow down, free fatty acids inhibit the action of insulin, and the production of glucose by hepatocytes persists in the same volume and subsequently increases. The described processes result in chronic hyperglycemia and a gradual decrease in the volume of insulin secretion by chronically stimulated β-cells, followed by the development of insulin deficiency, which underlies type 2 DM [8, 30, 76, 80].

Under IR conditions, the activity of serine–threonine protein kinase (mTORC2) in adipose tissue decreases; accordingly, MPC1 is depressed. Since mTORC2 is very significant in the indirect pathway of activation of immunomodulatory and tissue remodeling type (M2) macrophages, suppression of its effects shifts the balance toward increased reprogramming of macrophages into the M1 phenotype. Thus, IR acts as an independent factor in the development of inflammation in adipose tissue and, in combination with obesity, mutually aggravates the severity of this process [42, 71].

In addition, the synergism of COVID-19 and IR, which explains the increased risk of complications, is possibly due to the tropism of the virus to the same organs and tissues that are affected in type 2 DM. Lung dysfunction can probably be considered an equally significant mechanism that affects the severity of symptoms and the probability of complications in a disease caused by COVID-19. Excessive accumulation of visceral fat leads to an upward displacement of the diaphragm and a decrease in lung volume, which over time can cause airway collapse in the lower lung lobes. On the contrary, by stimulating the preganglionic parasympathetic fibers in the dorsal motor nucleus of the vagus nerve, insulin increases the reactivity of the airways. Cytokines block the post-receptor signaling pathway from the insulin receptor to its substrates and phosphoinositide 3-kinase (PI3K), thus interrupting the PI3K/AKT/mTOR signaling pathway that mediates the anabolic action of insulin. Accordingly, the production of nitric oxide (NO) in the vascular endothelium decreases. Moreover, the mediated signal transduction pathway through mitogen-activated protein kinases is not affected, which leads to the potentiation of its action and subsequently increased production of endothelin 1.

Systemic endothelial dysfunction results in an imbalance in the regulation of systemic BP and a high probability of chronic bronchial obstruction and bronchospasm [67].

The relationship between IR and COVID-19 course is bilateral. Probably, the virus has a tropism for pancreatic β-cells on the membrane surface. This finding can be due to the expression of angiotensin-converting enzyme 2 (ACE2) on the surface of their membranes. The spike protein of the virus has a high affinity for ACE2 receptors, which facilitate the transport of the virus into the cells and cause its high virulence, and in addition to pancreatic cells, ACE2 is produced by endothelial cells of the pulmonary arteries, heart, nervous system, kidneys, intestines, and blood vessels, which ensures the tropism of the virus to them.

According to some data, the ducts and pancreaticoduodenal arteries are also targets of the virus, which contributes to the negative effect of COVID-19 on the pancreas. Subsequently, β-cell dysfunction is noted, and insulin secretion is impaired [38, 48].

Furthermore, studies of animal models demonstrated the significance of ACE2 deficiency in the progression of β-cell proliferation disorders, their increased oxidative stress, and consequently an increase in the severity of hyperglycemia. This aspect may induce additional difficulties in choosing the optimal treatment approach [62, 72]. The effects of IR leading to a persistent increase in systemic BP, in addition to NO deficiency and endothelial dysfunction, include hyperactivation of the renin–angiotensin–aldosterone system (RAAS) and increased levels of sodium and potassium ions inside the cells. These causes of AH development are a consequence of the impossibility of suppressing angiotensinogen expression in the proximal tubules of the kidneys under the action of insulin in the case of IR. Ultimately, the tendency of vessels to constrict increases, which worsens endothelial damage, causes hypervolemia, and redistributes blood flow to the cardiopulmonary region. Moreover, a mechanical component mediated by an increase in the amount of perirenal adipose tissues contributes to the increase in pressure in the renal arteries and excessive RAAS activation [16, 26].

ACE2, associated with the S-protein of SARS-CoV-2, loses its functions, and when the RAAS is hyperactive, the production of the free enzyme is suppressed. This process causes excessive production of angiotensin (AT) II and impaired insulin secretion. The latter circumstance leads to the development of absolute insulin deficiency and to an earlier need for insulin replacement therapy [20, 91].

The ability of AT II to stimulate the production of procollagen through AT 1 receptors in case of lung damage is essential in the pathogenesis of severe COVID-19, in enhancing the expression of tissue factor and platelet growth factor with an increase in platelet aggregation, and in inducing the growth of smooth muscle cells of the vascular wall and IL-6 transcription. Thus, AT II excess contributes to the progression of the pro-inflammatory activity of cytokines, AH, atherosclerotic and thrombotic vascular lesions, and worsening prognosis in COVID-19 [55].

The progression of the severity of metabolic disorders is associated with increased levels of atherogenic lipoproteins and TG and decreased blood concentration of HDL. First, this is due to the excessive intake of non-esterified fatty acids, the potentiation of the action of TG synthetase and 3-hydroxy-3-methyl-CoA reductase, followed by an increase in the production and accumulation of TG in adipose tissue in abdominal–visceral obesity. Because of IR, the activity of endothelial lipoprotein lipase (LPL) also decreases, which disrupts the utilization of very LDL (VLDL) and slowdown HDL formation, as one of the sources of their production is the hydrolysis of VLDL. The presence of hyperinsulinemia creates conditions for the accelerated breakdown of HDL. Dyslipidemia occurs as a natural result [14, 66].

The decrease in the concentration of cholesterol and its fractions in the blood detected in patients with COVID-19 may be associated with the negative effects of pro-inflammatory cytokines, mainly TNF-α, IL-1, and IL-6, on the enzymatic activity of LPL with the formation of antibodies to it [32]. Moreover, an increase in the level of free radicals in infected cells contributes to lipid peroxidation; therefore, for an accurate assessment of lipid metabolism during examinations, the concentration of oxidized LDL in the blood serum of patients should be measured. This circumstance was not considered in most meta-analyses. Another important issue can be considered an impairment of the permeability of the vascular wall, which explains the increased volume of intra-alveolar exudate and decreased levels of lipoproteins in the blood plasma with the disease progression. Based on the available information on the effect of SARS-CoV-2 on the lipid profile, the lipid profile panel in patients with COVID-19 can be considered a marker of the disease course [83].

Thus, the pathogenesis of COVID-19 has mechanisms of action similar to those of MS, which, when these two conditions are combined, provides a more pronounced clinical presentation of the disease, a high risk of complications, and an adverse outcome.

TREATMENT

To date, there are no unified recommendations for the treatment of COVID-19 in patients with metabolic disorders. However, given the commonality of pathophysiological processes, several characteristics can be distinguished.

An anti-obesity treatment can be a good option to improve the prognosis of COVID-19. An integrated approach aimed at modifying lifestyle is the most effective, as it consists in the formation of adequate attitudes regarding eating behavior and changing the diet in combination with physical activity that meets the standards.

In the medical treatment of obesity in the Russian Federation, orlistat, liraglutide, and sibutramine are used alone or in combination with metformin. As a selective inhibitor of pancreatic lipase, orlistat reduces intestinal fat absorption. Liraglutide, an analog of glucagon-like peptide 1 (GLP-1), stimulates the neurons of the ventromedial nucleus while exerting an inhibitory effect on the neurons of the lateral nucleus of the hypothalamus, slows down gastric motility, and increases the activity of glucose-dependent insulin secretion. Sibutramine, which is an inhibitor of the reuptake of serotonin, norepinephrine, and dopamine, contributes to an earlier onset of satiety and a decrease in the amount of food consumed.

These drugs are indicated if a patient with MS has BMI >27 kg/m^2. In this case, the criteria for evaluating the efficiency of the measures taken will be a decrease in body weight by ≤5% in the absence of an established type 2 DM, or >3% of the initial weight in the presence of diabetes after a 3-month course of the drug. If the expected effect was not achieved or the BMI was >40 mg/kg^2, bariatric surgery should be decided [4].

According to clinical cases, the prescription of insulin therapy in patients with type 2 DM with moderate and severe COVID-19 worsened the prognosis. The retrospective studies of this issue revealed a decrease in mortality rates among individuals who received metformin as the main hypoglycemic therapy. On the contrary, given the limited amount of information, the accuracy of the results may be questionable, since the need for insulin replacement therapy is often noted in more severe type 2 DM. The pharmacological effect of metformin, which consists in the activation of the PI3K/AKT/mTOR signaling pathway, may affect adversely the penetration of the virus into target cells. The anti-inflammatory effect of the drug may also play a role in preventing multisystem inflammatory syndrome. Some preclinical studies have shown a decrease in the severity of pulmonary fibrosis with metformin, which supports the expediency of choosing this drug for glycemic control in presence of COVID-19 [34, 68–70].

The use of sulfonylurea drugs is associated with the risk of hypoglycemic conditions in patients treated in the ICU and those who are malnourished. The ability of drugs of this group to block KATP channel receptors increases the risk of damage to endothelial cells of the heart, and its tropism is characterized for SARS-CoV-2. Considering the circumstances described, patients with mild and moderate COVID-19 should choose new dosage forms that bind selectively to pancreatic β-cell receptors. This will help eliminate the expected negative effects [36, 90].

The use of sodium-glucose transporter (SGLT2) inhibitors is associated with a high risk of euglycemic ketoacidosis; thus, their use in patients requiring intensive care is also undesirable. Since SGLT2 increases lactate concentrations and lowers intracellular pH, reducing the viral load, their administration can theoretically be an adjunct to antiviral therapy [25].

GLP-1 receptor agonists can suppress the production of TNF-α, IL-1β, and IL-6 and inhibit the formation of reactive oxygen species, providing anti-inflammatory and protective effects on the vascular endothelium. Therefore, this group of drugs can be regarded as one of the preferred options for hypoglycemic therapy. Receptors activated by peroxisome proliferators have an anti-inflammatory effect because of their active expression in macrophages, thereby reducing the secretion of TNF-α, IL-1β, and IL-6, and potentiating effect on ACE2 production. Thus, the prescription of this group of drugs probably reduces lung damage and reduces the risk of lethal outcomes [19].

Dipeptidyl peptidase 4 (DPP-4) inhibitors are beneficial in cases of severe infections because they can be used even in patients with impaired renal function and have a low risk of hypoglycemia. The results of prospective studies indicated a low incidence of hypoglycemic complications and the achievement of more adequate glycemic control when using drugs of this group in combination with lower doses of insulin than with bolus administration of basal insulin [38]. As it has an affinity for the receptor-binding domain of the S-protein, DPP-4 can be a target of SARS-CoV-2, thereby reducing the viral load [47]. In summary, in cases of insulin deficiency, combination treatment with antihyperglycemic drugs will presumably balance the clinical benefits in the treatment of type 2 DM

and viral infection and the negative effects of insulin therapy.

COVID-19 necessitates a careful choice of optimal antihypertensive therapy, since ACE inhibitors and AT II receptor blockers can theoretically contribute to an aggravated disease course. Most of the studies concerning this problem did not show a clear pattern between the use of these drugs and an increase in the risk for hospital treatment or lethal outcome. Although the medical community does not have a clear position on this issue, most clinicians prefer to prescribe other groups of antihypertensive drugs to AH patients diagnosed with COVID-19. Otherwise, in the absence of the ability to stabilize BP with alternative treatment options, patients continue to take ACE inhibitors and AT II receptor blockers [68].

The use of lipid-lowering therapy in COVID-19 remains debatable. Data presented in the previous sections showed a clear correlation between the complicated course of the coronavirus infection and the blood plasma level of lipoproteins. Most of the arguments supporting the cessation of drugs that contribute to lipid metabolism normalization are based on disease pathogenesis and statistical indicators. However, some studies have demonstrated no negative influence on the course and outcome of COVID-19. By contrast, a case–control study showed a relatively lower hospitalization rate in the ICU of patients treated with statins [56].

Based on the assessment of a large amount of information, Iqbal et al. [44] made the following recommendations:

1) Patients with confirmed COVID-19 should continue to adhere to the recommended diet and lifestyle and take lipid-lowering drugs.

2) Treatment with lipid-lowering drugs can be temporarily suspended if oral administration is impossible because of the severity of the patient's condition.

3) In cases requiring anticoagulant therapy, an assessment of drug interaction with the hypoglycemic agent being taken is recommended.

4) Drug treatment should be discontinued or the dose reduced if laboratory parameters change, namely, an increase in the level of creatine kinase 10 times higher than the upper limit of the reference values in the absence of relevant symptoms or five times with the appearance of clinical manifestations, i. e., at least 3-fold increase in the blood concentrations of alanine aminotransferase and aspartate transaminase compared with the upper normal limit.

5) If a pronounced potentiating effect of the drugs taken is suspected, the possibility of reducing the dose or finding an alternative is recommended.

6) If symptoms of myositis occur during statin use, monitoring of the kidney function is recommended.

7) In the presence of clinical or biochemical changes indicating the development of myopathy, ongoing treatment with fibrates should be suspended.

8) If acute renal injury with a decrease in the estimated glomerular filtration rate is suspected during fibrate therapy, the drug intake should be discontinued.

9) If the patient is in a critical condition, omega 3 polyunsaturated fatty acids do not require cancellation.

10) If it is impossible to assess the risk of cardiovascular complications, given that interference with drug absorption is possible, cancellation of bile acid sequestrants is recommended.

11) As the efficiency of niacin is not proven in the prevention of cardiovascular complications, the use of the drug should be temporarily discontinued.

12) Lipoprotein apheresis is safe and should be continued if it is technically feasible.

13) If the treatment is suspended, after stabilization of the patient's condition, additional personalized assessment of the expected risks and benefits of resuming lipid-lowering therapy is recommended [10].

Conflicting results are demonstrated by data from a study of the efficacy and safety of antiviral therapy prescribed to patients with MS. Chloroquine can inhibit the replication of SARS-CoV-2 due to glycosylation of ACE2 by blocking the connection between the virus and receptor and resulting increase in endosomal pH. However, this antiviral drug negatively affects *QT* interval elongation and development of retinopathy and cardiovascular disorders, which restricts its use in patients with MS.

Hydroxychloroquine (HCQ) also increases intracellular pH and inhibits lysosomal activity in antigen-presenting cells. This process reduces T-cell activation, differentiation, and expression of costimulatory proteins and cytokine production. In the cytoplasm, it interferes with the synthesis of viral nucleic acids, probably by suppressing the immune system hyper-reactivity caused by the virus. Combination therapy of HCQ with azithromycin for 6 days demonstrated the high efficiency of the chosen treatment approach. However, conflicting information about the safety of long-term use

of the drug prevents from regarding HCQ as a drug for widespread use in the treatment of COVID-19.

The expediency of prescribing favipiravir to treat COVID-19 is attributed to the inhibition of RNA polymerase activity. The antiretroviral drugs lopinavir and ritonavir have demonstrated high *in vitro* activity against other types of coronaviruses by inhibiting 3-chymotrypsin-like protease. However, available data on the clinical efficacy of these antiviral drugs are insufficient to make definite decision in favor of their choice. Remdesivir has a broad-spectrum antiviral activity against filoviruses, paramyxoviruses, pneumoviruses, and coronaviruses. *In vitro* studies have shown the ability of remdesivir to inhibit SARS-CoV-2 replication in the lungs, with a wide range of side effects detected during patient follow-up requiring a comprehensive clinical evaluation of patients with complications associated with MS.

Plasma immunoglobulins from convalescent or hyperimmune individuals can be considered a potential adjuvant therapy for COVID-19, and its use is justified by the ability of antibodies from recovered patients to help in the immune response against the virus or become the main method of prevention, especially for patients with metabolic disorders. Nitazoxanide (the drug is not registered in the Russian Federation) has broad antiviral activity and a relatively favorable safety profile. *In vitro* studies have demonstrated its antiviral activity against SARS-CoV-2, but there is no conclusive evidence; thus, further study of the drug and therapeutic option for COVID-19 are necessary.

Additional difficulties in determining the treatment approach may arise when prescribing anticoagulant therapy and glucocorticosteroids. This is associated with high risks of thrombotic complications, which simultaneously occur in both the presence of MS and the development of an infectious process caused by SARS-CoV-2. The latter event is explained by high levels of inflammatory mediators and immunoglobulins, resulting in increased blood viscosity. When performing APV and catheterization in the central vein of patients with metabolic disorders, special care should be exercised owing to the high probability of additional damage to the endothelium. In turn, glucocorticosteroids are indicated to reduce the severity of the inflammatory process in the lungs. This advantage can be leveled because of the side effects, particularly hyperglycemia and a secondary infection, which is a significant limitation for prescribing glucocorticosteroids to patients with MS [22].

According to the Russian Ministry of Health, in comparison with the adult population, children are affected by COVID-19 with less pronounced clinical symptoms, require hospitalization less often, and have milder disease, which, however, does not exclude severe cases. Currently available data indicate that children represent up to 10% of patients infected with SARS-CoV-2 and up to 2% of patients are diagnosed with COVID-19. In the Russian Federation, 6%–7% of registered cases of COVID-19 are registered in children [1]. Treatment regimens for children with COVID-19 are determined by the severity of the disease course which, like in adults, varies from asymptomatic to critical form with multisystem inflammatory syndrome, cytokine storm, Kawasaki-like syndrome, and septic complications. Overweight, obesity, DM, and impaired glucose tolerance, as in adult patients, are risk factors for a severe disease course, which determines the composition and volume of therapy, such as the use of oxygen therapy, antiviral agents, anticoagulants, glucocorticosteroids, immunoglobulin, antibacterial drugs [54].

Furthermore, researchers are concerned by the increased risk of development and progression of overweight and obesity in the population during long-term anti-epidemic measures, leading to decreased physical activity level, hypodynamia, disruption of the daily regimen, and deformation of the structure of leisure and social ties [5]. The long-term replacement of positive motivation for success in sports (including team sports with a predominance of aerobic loads) by a socially approved behavior model that focused on fulfilling restrictive requirements and avoiding risks is hazardous at the stage of personality formation.

During the anti-epidemic period, children are the most vulnerable in losing the most important components of a healthy lifestyle, particularly rational and healthy eating habits, regulation of “screen” time, responsible planning of study time and leisure, and regular and intense physical activities [65, 79, 84]. Thus, a long restrictive period requires additional attention from doctors, teachers, and rehabilitation specialists to the problem of maintaining the adherence of children and parents to a healthy lifestyle.

PATIENT REHABILITATION

Rehabilitation is necessary for patients who have had severe and moderate infections, with the subsequent development of complications and organ failure. Rehabilitation measures should be person-

alized and focused on each problem and need of the patients. Recovery activities can be conducted in a rehabilitation center or at home, and delayed recovery can be performed in healthcare and sanatorium resort institutions. In morbid obesity, treatment, rehabilitation, and care of patients in the ICU are often complicated because of difficulties in transportation, log-roll maneuvers, and imaging examinations [3].

The generalization of data on the rehabilitation of patients with severe disease in the ICU helped identify the so-called syndrome of the consequences of intensive care in patients with COVID-19. It is manifested by a complex of somatic, neurological, and sociopsychological changes in the conditions of patients with COVID-19 and is most often noted with prolonged APV use by older patients with concomitant diseases, which affects the severity of respiratory, neurological, and musculoskeletal disorders. The most common manifestations of the syndrome include polyneuropathy, difficulty dishabituation from APV, shortness of breath, atrophy of respiratory muscles, general weakness, impaired sensitivity, diaphragmatic discomfort, decreased or absent tendon reflexes, dysphagia, anxiety, depression, and cognitive and other mental disorders [2].

The syndrome of ICU consequences often co-occurs with post-traumatic stress symptoms such as psycho-emotional lability, unpleasant memories, anxiety, fear attacks, sleep disorders, depression, and reserved demeanor. According to various estimates, 20% of patients who recover from COVID-19 have a nearly two-fold increase in the risk of developing dementia and mental disorders. This is due to both direct and indirect consequences of the disease. The reality of such a prognosis is confirmed by the analysis of electronic medical records of over 60 thousand patients who recovered from COVID-19. In the first 3 months after recovery, one in five patients showed the first signs of anxiety, depression, and insomnia [45].

Rehabilitation of patients with COVID-19 includes several aspects, namely, medical, physical, educational, and psychological aspects. The medical aspect includes examination, assessment of the clinical condition, identification and correction of traditional cardiovascular risk factors, and provision of appropriate drug therapy. The psychological aspect of rehabilitation is associated with the need for the patient to psychologically adapt to the disease, increased resistance to stressful situations, and, if necessary, treatment of anxiety and depressive disorders [3].

CONCLUSION

Patients with MS are considered one of the cohorts most vulnerable to the adverse course of infection caused by SARS-CoV-2. The event is mainly caused by the common application points of the mechanisms for the development of metabolic changes and COVID-19. The combined effect on target organs causes significant damage to the body and difficulties in choosing the most effective and, which is no less significant in a particular situation, safe treatment approach. The high probability of complications and consequently the need for intensive care determine the high demand for rehabilitation measures. The results of studies on the issues raised and the implementation of related tasks indicate the need for a personalized approach.

ADDITIONAL INFORMATION

Author contributions. All authors confirm that their authorship complies with the ICMJE criteria. All authors have made a significant contribution to the development of the concept, research, and preparation of the article; they read and approved the final version before its publication.

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