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Adipokine imbalance and its role in the pathogenesis of novel coronavirus infection

Bespalova I.D., Mitrichenko U.M., Kalyuzhin V.V., Koroleva E.S., Koshchavtseva Yu.I., Romanov D.S., Pershina D.E.

Siberian State Medical University
2, Moscow Trakt, Tomsk, 634050, Russian Federation

ABSTRACT

The review summarizes and analyzes the results of major foreign studies on the role of adipokine imbalance in the development of a severe course and complications of novel coronavirus infection (COVID-19). Adipokines are biologically active compounds produced by adipose tissue cells and involved in the regulation of metabolism and the functioning of the immune system.

Obesity is a proven risk factor for severe COVID-19 due to high hormonal and metabolic activity of visceral adipose tissue. A deep understanding of COVID-19 pathogenesis from the point of view of the role of adipokine imbalance in it can provide the grounds for the development of effective pathogenetic approaches to the prevention of a severe course and complications of novel coronavirus infection.

Keywords: novel coronavirus infection, SARS-CoV-2, metabolic syndrome, obesity, adipokines, adipokine imbalance

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Дисбаланс адипокинов и его роль в патогенезе новой коронавирусной инфекции

Беспалова И.Д., Митриченко У.М., Калюжин В.В., Королева Е.С., Кощавцева Ю.И., Романов Д.С., Першина Д.Е.

Сибирский государственный медицинский университет (СибГМУ)
Россия, 634050, г. Томск, Московский тракт, 2

РЕЗЮМЕ

В обзоре обобщены и проанализированы результаты крупных зарубежных исследований, касающихся изучения роли адипокинового дисбаланса в развитии тяжелого течения и осложнений новой коронавирусной инфекции (COVID-19). Адипокины – биологически активные соединения, которые вырабатываются клетками жировой ткани и участвуют в регуляции обмена веществ и работы иммунной системы.

Известно, что ожирение является доказанным фактором риска тяжелого течения COVID-19 в связи с высокой гормональной и метаболической активностью висцеральной жировой ткани. Глубокое понимание

✉ *Bespalova Inna D.,* innadave@mail2000.ru

патогенеза COVID-19 с позиций участия в нем адипокинового дисбаланса может лечь в основу разработки эффективных патогенетических подходов к профилактике тяжелого течения и осложнений новой коронавирусной инфекции.

Ключевые слова: новая коронавирусная инфекция, SARS-CoV-2, метаболический синдром, ожирение, адипокины, адипокиновый дисбаланс

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

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INTRODUCTION

Novel coronavirus infection (COVID-19), caused by the SARS-CoV-2 virus, has become a serious medical and social problem throughout the world, as confirmed by epidemiological studies in recent years [1]. COVID-19 has significantly affected the level and structure of disability and mortality among the working-age population [2]. Despite the fact that the World Health Organization (WHO) has declared the end of the pandemic, the incidence of COVID-19 remains significant. The infectious process in COVID-19 is manifested by a variety of symptoms and pronounced clinical presentation, from an asymptomatic course to fulminant forms of the disease [3]. The scientific community's understanding of the mechanisms of the SARS-CoV2 effect on the body continues to expand, and currently there are sufficient data indicating not only damage to the respiratory system, but also the involvement of other body systems in the pathological process [4].

The severity of the problem of COVID-19 is determined not only by the unprecedented level of prevalence, a trend toward a severe course, and the frequency of fatal complications, but also by the lack of a comprehensive understanding, due to the short observation period, of the leading links in the pathogenesis of this infection, which determine the prognosis. In the scientific literature of recent years, the search for predictors of the severe course and adverse outcomes of COVID-19, including mortality, has been widely discussed.

METABOLIC SYNDROME AS A RISK FACTOR FOR A SEVERE COURSE OF COVID-19

To date, a large amount of evidence has been accumulated convincingly indicating that the components of metabolic syndrome (MS) should be taken into account as predictors of a severe and complicated course of COVID-19. MS is characterized as a complex of metabolic, hormonal, and clinical disorders associated with a large number of socially sensitive chronic non-communicable diseases and also determines the severe course of a number of infections. Insulin resistance, dyslipidemia, abdominal obesity, and arterial hypertension (AH) are considered as the main components of MS. Each of these components underlies the development and the severe and complicated course of associated pathology, worsens the disease prognosis, and negatively affects the quality of life of patients [5].

The prevalence of MS in recent years has become pandemic in nature and is maintaining an upward trend, covering, according to recent estimates, up to 50% of the population in the Russian Federation [6]. Chronic systemic low-grade inflammation is considered to be one of the key pathogenetic factors that unites MS and associated diseases. This is illustrated by numerous studies showing a direct relationship of the level of systemic inflammation markers with the severity of metabolic disorders and the risk of developing a number of socially sensitive non-communicable diseases [5, 7].

Since the beginning of the COVID-19 pandemic, data have been accumulated on the impact of metabolic disorders on the course of the infection. Researchers' attention was drawn to the fact that the presence of obesity, AH, and carbohydrate metabolism disorders increased the risk of hospitalization and a severe course of COVID-19 [8, 9].

Thus, a cohort study conducted by J.L. Denson et al., including 29,040 patients hospitalized with COVID-19, revealed that the presence of MS significantly increased the risk of hospitalization

in the intensive care unit (ICU), the frequency of using mechanical ventilation, and the development of acute respiratory distress syndrome (ARDS) and death. At the same time, the severity of metabolic disorders determined the risk of complications [10]. It was found that MS proved to be a more significant prognostic factor for severe COVID-19 than each of its components separately [11]. However, each of the components makes its own negative contribution and aggravates the course of the infectious process, which is also confirmed by the results of a number of studies. A 2021 meta-analysis combining data from 186 studies showed an increase in the relative risk of death from COVID-19 in patients with diabetes mellitus (DM) by 54%, in patients with hypertension – by 42%, and in patients with obesity – by 45%. [12].

CARBOHYDRATE METABOLISM DISORDERS AND COVID-19

Long before the COVID-19 pandemic, results were published characterizing hyperglycemia and DM as independent predictors of a severe course and mortality for respiratory infections, such as SARS [13]. As the COVID-19 pandemic spread, researchers from different countries pointed out that the presence of DM significantly increases the risk of death in COVID-19 [14–16]. It was noted that not only DM was associated with the development of adverse outcomes, but also an increase in fasting blood glucose levels was associated with a high risk of mortality after adjustments for age, gender, and comorbidities [17].

The results from meta-analyses also showed that hyperglycemia at admission was a strong independent predictor of a severe course and mortality in COVID-19. In particular, an increase in glucose concentration by 1 mmol / l increased the risk of a severe disease course by 33% [18, 19]. It is now known that HbA1c level is also associated with increased mortality and severity of COVID-19 [20].

ARTERIAL HYPERTENSION AND COVID-19

An analysis of multiple observational studies found that the risk of death for patients with AH during COVID-19 was 11% higher than for patients without AH [12]. Some reports have suggested that AH may represent a risk factor for increased susceptibility to COVID-19 infection, a more severe course of the disease, and increased mortality. However, the independent role of AH remains a matter of debate, since this syndrome is often associated with older age and other cardiovascular risk factors in the general population, which may also aggravate the course of COVID-19. It is believed that high and uncontrolled systolic blood pressure may contribute to a more severe course of COVID-19, likely due to the presence of vascular remodeling, which may exacerbate endothelial dysfunction, endothelial lesions, and endotheliitis caused by COVID-19 [21].

DYSLIPIDEMIA AND COVID-19

Researchers' attention was drawn to the nature of dyslipidemia, which has distinctive features in COVID-19. At the beginning of the pandemic, Chinese scientists described changes in the lipid profile characteristic of COVID-19: a significant decrease in the level of total cholesterol (TC), low-density lipoproteins (LDL), and high-density lipoproteins (HDL) in the blood serum compared to the controls [22]. At the same time, hypolipidemia, which occurred in patients even with a mild infection, tended to progress as the severity of COVID-19 increased [23, 24]. Another group of researchers noted that patients admitted to the ICU had higher triacylglycerol (TAG) levels [25]. Subsequently, as clinical data accumulated, large meta-analyses were conducted that confirmed the association of dyslipidemia with the severity of COVID-19 and the risk of death [26, 27].

OBESITY AND COVID-19

Obesity as an unfavorable prognostic factor in respiratory infectious diseases was considered long before COVID-19. Back in 2009, during the influenza A (H1N1) pandemic, obesity was first characterized as a predictor of a severe disease course and high mortality in infected individuals [28]. In further clinical studies of H1N1 flu, obesity was associated with an increased risk of hospitalization, transfer to ICU, and a need for mechanical ventilation [29, 30]. Since the beginning of the COVID-19 epidemic, researchers have noted that a significant proportion of SARS-CoV-2-infected patients with respiratory failure admitted to the ICU were overweight. The strong relationship of abdominal obesity with adverse outcomes of COVID-19 infection (the risk of hospitalization, the severity of clinical and paraclinical symptoms, the development of respiratory failure, the need for mechanical ventilation, and mortality) has been confirmed by a number of independent studies conducted in different countries [31–33]. A meta-analysis of several large-scale epidemiological studies suggests that with increasing body weight, the severity of the disease increases significantly [34–36].

Therefore, the association of obesity with adverse clinical outcomes from COVID-19 is robust across the board and persists even after adjusting for confounding variables, such as age, sex, and comorbidity. Various mechanisms are currently being discussed to explain why obese patients are most susceptible to respiratory infections, including COVID-19. The role of abdominal obesity in the pathogenesis of undesirable outcomes of associated diseases is explained by high endocrine and metabolic activity of adipose tissue. Visceral adipose tissue secretes biologically active substances in large quantities, such as adipokines. They realize their systemic effect by participating in the regulation of a variety of body functions [37]. The biological effects of adipokines and the molecular mechanisms of their action require careful study [28]. Recently, close attention of researchers has been directed to studying the role of adipokine imbalance not only in the pathogenesis of diseases associated with MS, but also in the mechanisms of development of COVID-19.

ADIPOKINE IMBALANCE AND COVID-19

The most studied adipokines to date include leptin and adiponectin.

Leptin is an adipokine synthesized primarily by adipocytes in response to food intake, acting as a signaling molecule for the brain in the regulation of appetite and metabolism. Circulating leptin levels are directly proportional to body adipose tissue mass and are altered under conditions of both chronic negative and positive energy balance, whereby undernutrition promotes hypoleptinemia, and obesity promotes hyperleptinemia [39]. In addition to its main role in regulating appetite and maintaining body weight due to the induction of anorexigenic factors, suppression of orexigenic neuropeptides in the hypothalamus, and influence on energy metabolism, leptin plays an important role in the functioning of the immune, hematopoietic, neuroendocrine, and reproductive systems [40]. Leptin is characterized by many researchers as an inducer of inflammation and oxidative stress, since its level in the blood is associated with the proinflammatory and prooxidant activity of immunocompetent cells in the blood and adipose tissue [41–43]. In this regard, the scientific interest in the role of this adipokine in the mechanisms of COVID-19 development is justified.

Thus, it was found that the average level of leptin in the blood was higher in patients with novel coronavirus infection who were critically ill, in contrast to a group of patients with critical illness not associated with COVID-19, while leptin levels correlated with body mass index (BMI) [34, 44]. Along with the level of proinflammatory cytokines, the level of leptin is closely associated with the progression and severity of the infectious process [45] and the need for transfer to ICU [46]. Changes in the leptin concentration in the blood of patients with COVID-19 were determined: peak values were observed on day 1 with a gradual decrease over the next 28 days of illness, which coincided with the changes in the level of inflammatory biomarkers interleukin (IL)-1β and tumor necrosis factor (TNF)α [47].

However, a number of researchers studying the pathogenetic role of leptin did not find statistically significant associations of leptin levels with either the severity of the disease or inflammatory factors (C-reactive protein (CRP), IL-6) in the blood of patients [48], or with the need to transfer patients with COVID-19 to the ICU [25], as well as with in-hospital mortality [49]. Researchers' attention was also drawn to the fact that the concentration of leptin was significantly higher in women than in men, which confirms the results of other authors who showed gender characteristics of hyperleptinemia [50].

Adiponectin is a polypeptide that is mainly produced by subcutaneous adipose tissue and exhibits a wide range of protective effects: increasing insulin sensitivity, oxidizing fatty acids in adipose tissue and free fatty acids in skeletal muscles, reducing glucose release from the liver, increasing glucose uptake, and activating adipogenesis [51, 52]. The effects of adiponectin are realized through its receptors, which are found in adipose tissue, liver, and skeletal muscles [53, 54]. The level of adiponectin increases with a decrease in body weight in the context of taking antidiabetic drugs; in obesity, insulin resistance, and inflammation, its secretion decreases [55]. It is known that this adipokine exhibits anti-atherosclerotic effects, inhibiting the migration of monocytes / macrophages into the vessel wall and preventing the formation of foam cells, as well as a selective anti-inflammatory effect [56]. The anti-inflammatory effects of adiponectin were confirmed by negative relationships between its concentration and the level of some proinflammatory cytokines and markers of oxidative stress [50, 57–59].

Scientific interest in the role of adiponectin in the pathogenesis of COVID-19 has been demonstrated by a large number of publications. Some studies in which the level of adiponectin was determined once

at admission did not show its relationship with the severity of the disease or with adverse outcomes in COVID-19 [25, 48, 60, 61]. Italian researchers found that serum adiponectin levels were significantly lower in hospitalized patients with COVID-19 compared to healthy controls. Moreover, patients in both groups differed significantly in BMI, which may explain the observed difference in adiponectin concentrations. It was also noted that high molecular weight (HMW) oligomeric complexes, considered to be the most active form of adiponectin, were negatively correlated with the degree of lung injury (as measured by ultrasound, LUS score), while serum adiponectin levels generally did not show a prognostic value for adverse outcomes in patients with COVID-19 [44].

Danish researchers showed that the level of adiponectin in patients with community-acquired pneumonia of various etiologies, including SARS-CoV-2, despite higher values of inflammatory biomarkers in patients with novel coronavirus infection, did not differ significantly [62]. Experts from the University of Virginia School of Medicine (USA) found that patients with COVID-19 complicated by respiratory failure had lower adiponectin values, in contrast to patients with respiratory failure associated with infections of other etiologies [63]. The study conducted within the CRACoV-HHS project in Poland included the assessment of the levels of adiponectin and other cytokines in a cohort of patients with COVID-19 with varying degrees of severity not only at admission, but also on day 7 and 28 of hospitalization. Severe infection was associated with low adiponectin values throughout the observation period and increased levels of inflammatory biomarkers (TNFα, IL-1β, PTX3) [47]. Dutch colleagues in a multicenter prospective study found that patients with severe and extremely severe COVID-19 had lower adiponectin values [64]. In a recently published retrospective study, doubling circulating adiponectin levels was associated with a 38% reduction in the odds of 90-day mortality (OR 0.62, CI 0.43–0.89) and a 40% reduction in the risk of developing respiratory failure (OR 0.60, CI 0.42–0.86) [65]. This reflects the protective and anti-inflammatory properties of adiponectin, previously described by many researchers, and may serve as a reason for continuing studies in larger cohorts of patients.

Resistin is a protein predominantly synthesized by monocytes and macrophages [66]. Currently, resistin is considered as an adipokine involved in the formation of insulin resistance and inflammatory responses [67]. Resistin is believed to influence obesity and insulin homeostasis through paracrine and endocrine signaling pathways. Resistin has a proinflammatory effect because it stimulates the expression of TNFα and IL-6 by mononuclear leukocytes [68], and it is considered as a marker of inflammation in atherosclerosis [69]. Studies on the effects of resistin in individuals with metabolic disorders, including obesity, have shown conflicting results [70, 71].

In few studies examining the role of resistin in the pathogenesis of the inflammatory response in COVID-19, it has shown itself to be a promising marker that can be considered as a predictor of not only the severity of COVID-19, but also of adverse outcomes. A number of researchers found a significant increase in the level of resistin in the serum of patients with COVID-19, which correlated with the level of proinflammatory cytokines, the severity of the disease, and the frequency of adverse outcomes, including mortality [44, 47, 61, 64, 72]. Resistin levels were associated with the severity of clinical symptoms, the need for oxygen therapy, and the need for mechanical ventilation [73]. Besides, it was also associated with a worse prognosis of COVID-19 and was characterized as a diagnostically significant predictor for transfer of patients to ICU [74].

Chemerin is a protein that is synthesized primarily by hepatocytes and adipocytes. Researchers' interest in this adipokine has appeared relatively recently. It was found that chemerin is involved in the regulation of a large number of biological processes: it affects the differentiation of adipocytes and regulates adipogenesis, glucose homeostasis, oncogenesis, inflammation, angiogenesis, myogenesis, and migration of immunocompetent cells, acting as a chemoattractant [75–79]. The question of whether chemerin is a pro- or anti-inflammatory protein is the subject of active scientific debate, as conflicting results have been obtained in cell culture studies and biological models [80, 81], which opens up prospects for further basic research.

Currently available studies on chemerin in COVID-19 also show mixed results. Thus, despite the fact that in patients with novel coronavirus infection, the concentration of chemerin in the blood serum was significantly lower than in healthy people, the relationship with the severity of clinical symptoms, the severity of the course, and the need for hospitalization in the ICU has not been established [82]. Polish scientists drew attention to the fact that patients with severe and moderate COVID-19 had the

lowest concentrations of chemerin in the blood on day 7, while in patients with mild COVID-19, the level of chemerin did not change throughout the observation period. Researchers believe that the decrease in the chemerin concentration one week after the onset of symptoms may be associated with inflammatory activity in severe COVID-19 [47].

Belgian researchers found the opposite results: the concentration of chemerin in the blood was significantly higher in patients hospitalized in the ICU. Moreover, chemerin levels were associated with the severity of the disease and positively correlated with inflammatory biomarkers, such as CRP and TNFα. The univariate and multivariate logistic regression analysis showed that high chemerin levels on day 14 of hospitalization were an independent risk factor for death [83].

CONCLUSION

Despite the great interest of the scientific community in studying the role of adipokine imbalance in the mechanisms of development of COVID-19 and a significant number of publications on this topic, contradictory results associated with different study designs, the relevance of the novel coronavirus infection, and the need to search for diagnostically significant predictors of adverse outcomes open up prospects for further basic research in this area. A deep understanding of the pathogenesis of this infection from the standpoint of the role of adipokine imbalance in it can form the grounds for the development of effective pathogenetic approaches to the prevention of severe disease and complications.

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Authors' information

Bespalova Inna D. – Dr. Sci. (Med.), Head of the Division of Introduction into Internal Diseases with a Course in Therapy, Siberian State Medical University, Tomsk, innadave@mail2000.ru, http://orcid.org/0000-0002-4513-6329

Mitrichenko Ulyana M. – Post-Graduate Student, Division of Introduction into Internal Diseases with a Course in Therapy, Siberian State Medical University, Tomsk, strashkovaum@gmail.com, http://orcid.org/0000-0001-6091-4849

Kalyuzhin Vadim V. – Dr. Sci. (Med.), Professor, Head of the Advanced Therapy Division with a Course in Rehabilitation, Physiotherapy and Sports Medicine, Siberian State Medical University, Tomsk, kalyuzhinvv@mail.ru, http://orcid.org/0000-0001-9640-2028

Koroleva Ekaterina S. – Dr. Sci. (Med.), Professor, Neurology and Neurosurgery Division, Siberian State Medical University, Tomsk, kattorina@list.ru, http://orcid.org/0000-0003-1911-166X

Koshchavtseva Yuliya I. – Assistant Lecturer, Division of Introduction into Internal Diseases with a Course in Therapy, Siberian State Medical University, Tomsk, kossy09@mail.ru, http://orcid.org/0000-0001-5260-4832

Romanov Dmitriy S. – Post-Graduate Student, Division of Introduction into Internal Diseases with a Course in Therapy, Siberian State Medical University, Tomsk, romanovds92@yandex.ru, http://orcid.org/0009-0002-2028-4963

Pershina Diana E. – 6-year Student, Pediatric Department, Siberian State Medical University, Tomsk, dianapershina2000@gmail.com, http://orcid.org/0000-0003-3202-4579

(✉) **Bespalova Inna D.,** innadave@mail2000.ru

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