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Negative Impact of Covid-19 on the Endocrine System

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Abstract: The SARS-CoV-2 virus has rapidly spread throughout the world, causing an unprecedented pandemic. Due to the novelty of the disease, the potential impact on the endocrine systm is currently not entirely clear. It is known that the virus uses the extracellular domain of angiotensin-converting enzyme 2 (ACE-2) and the transmembrane protein TMPRSS2 to infect cells. It is assumed that the widespread expression of ACE-2 and TMPRSS2 may be the cause of various extrapulmonary complications of SARS-CoV-2, including endocrine ones. The most discussed are lesions, direct or indirect, of the endocrine pancreas, hypothalamic-pituitary-adrenal and hypothalamic-pituitary-thyroid axes, as well as possible long-term consequences associated with the function of the reproductive system. Shown that obesity and diabetes increase the risk of severe disease and mortality in COVID-19. Patients with transient hyperglycemia, as well as diabetes mellitus, have a higher risk of severe viral infection. The severity of the condition may be due to primary and secondary adrenal insufficiency of various origins. The most common consequences of the thyroid system in COVID-19 are euthyroid pathology syndrome, transient destructive thyroiditis, including subacute thyroiditis.

Keywords: SARS-CoV-2, COVID-19, endocrinopathies, diabetes mellitus, adrenal insufficiency.

Relevance. In March 2020, WHO declared COVID-19, caused by the SARS-CoV-2 virus, a pandemic. At the time of writing this publication, the incidence worldwide was more than 232 million cases. SARS-CoV-2 is an RNA virus from the coronavirus family, which also includes the SARS virus (SARS-CoV), which caused the SARS (severe acute respiratory syndrome) epidemic in 2002, and MERS (MERS-CoV), which caused Middle East respiratory syndrome 2012 All three single-stranded (+)RNA viruses belong to the genus Betacoronaviruses (*Betacoronavirus*) with a molecular weight of 26–32 kDa. Phylogenetically, SARS-CoV-2 is close to SARS-CoV, and therefore an attempt is possible to extrapolate the data obtained during the analysis of the SARS epidemic in 2002–2003 to the situation with COVID-19. The SARS-CoV-2 virus also causes acute pneumonitis and a number of extrapulmonary complications: cardiovascular, neurological, gastroenterological, skin, ophthalmological, reproductive, endocrine, etc. It is believed that coronaviruses use transmembrane proteins to penetrate cells. The most well-known and characterized receptor for SARS-CoV and SARS-CoV-2 is angiotensin-converting enzyme 2 (ACE-2), the extracellular domain of which is a surface receptor to which viruses bind using surface spike proteins (S-protein , spike protein) [1]. Besides, To enter the cell, SARS-CoV-2 requires TMPRSS2, a transmembrane protein from the serine protease family, which is necessary to activate the S protein of the virus. The possibility of

SARS-CoV-2 binding to another transmembrane protein, neuropilin-1, has been shown, which may also explain the high contagiousness of the new virus.

ACE-2 is widely expressed in various tissues, including the pancreas and thyroid glands, pituitary gland, adrenal glands, gonads, and adipose tissue, which may cause the development of extrapulmonary complications of the new coronavirus infection COVID-19, including complications of the endocrine system.

Pancreas

Cases of manifestation of diabetes mellitus (DM) with severe metabolic decompensation and diabetic ketoacidosis among patients with SARS-CoV-2, potentially healthy, without a history of diabetes, have been described. Considering the high expression of ACE-2 in the pancreas, the experience of the SARS epidemic, during which cases of newly diagnosed diabetes were also described, direct or indirect permanent damage to pancreatic b-cells can be assumed [11,12]. A decrease in the amount of ACE-2 due to infection with the SARS-CoV-2 virus is accompanied by an increase in the activity of angiotensin II, which, in turn, suppresses insulin secretion by b-cells of the pancreatic islets by connecting to AT-1 receptors[13]. Besides, local activation of the renin-aldosterone-angiotensin system in the pancreas leads to a decrease in insulin sensitivity and insulin resistance of tissues due to the suppression of insulin-mediated glucose transport into tissues[14,15]. To date, there is no convincing data on the direct effect of the virus on pancreatic β-cells, however, fulminant development and the absence of circulating autoantibodies may suggest the development of a special variant of diabetes caused by SARS-CoV-2 [16, 18]. On the other hand, COVID-19 may be a trigger for the manifestation of type 1 or type 2 diabetes. An international group of researchers in the field of diabetology has created a global registry of diabetes associated with COVID-19 - CoviDiab [17,19]. The purpose of the registry is to assess the prevalence and characterize newly diagnosed diabetes associated with COVID-19 in order to study its pathogenesis, therapy and outcomes. The registry also collects data on the development of severe metabolic decompensation of existing diabetes with the development of diabetic ketoacidosis, hyperosmolar hyperglycemic state and severe insulin resistance[20].

It has been shown that the presence of diabetes increases the risk of severe disease and mortality in COVID-19 [7,21]. Diabetes in COVID-19 is more common in hospitalized patients (31.8%) compared to outpatients (5.4%). A study in China including 72,314 patients found an overall COVID-19 mortality rate of 2.3%, with a mortality rate of 7.3% among patients with diabetes. An analysis of 1,590 patients with severe COVID-19 leading to hospitalization in intensive care units, mechanical ventilation, or death showed that 34.6% of patients had diabetes, while among patients with non-severe coronavirus infection, diabetes occurred in 14.3 % of cases[11,15].

A number of studies have been devoted to studying the role of hyperglycemia in the pathogenesis and course of acute respiratory viral infections [17]. A direct correlation of glucose levels with the concentration of the virus in the secretions of the respiratory tract has been shown. In in vitro studies, adding glucose to cell culture increased influenza virus replication. In animal models, DM has been associated with a number of structural changes in the lungs, including increased alveolar capillary membrane permeability and alveolar epithelial collapse. It has been shown that the level of IL-6 and D-dimer is significantly higher in patients with hyperglycemia than in normoglycemia. Patients with transient hyperglycemia, like those with diabetes, have a higher risk of severe viral infection. And glycemic control may have a positive effect in patients with concomitant diabetes in COVID-19[18].

Hypothalamic-pituitary system

Few studies are available on damage to the hypothalamic-pituitary axis during SARS infections. High expression of ACE-2 and TMPRSS2 has been shown in the hypothalamus, especially in the paraventricular nuclei [18, 19]. Autopsy data and immunohistochemical studies of 5 patients with SARS-CoV showed a decrease in TSH- and ACTH-producing cells of the adenohypophysis [16]. A prospective study included 61 patients with SARS-CoV after 3 months. after recovery,

revealed signs of secondary adrenal insufficiency in 39% of patients, while 2/3 of them did not receive glucocorticoid therapy earlier in the course of the disease, and therefore the authors conclude about late complications of SARS-CoV and the development of hypophysitis [11]. In addition, among the examined patients, central hypothyroidism was detected in 4.9%, in two patients - in combination with hypocortisolism.

A group of Chinese researchers isolated the SARS-CoV-2 virus in the cerebrospinal fluid of patients with COVID-19, thereby showing that the virus can infect the brain, including the hypothalamic-pituitary region [20].

Thus, damage to the hypothalamic-pituitary system could potentially be a direct consequence of SARS-CoV-2 infection or an indirect consequence of immune-mediated hypophysitis; another mechanism could be developing hypoxia.

Adrenal glands

Autopsy data from patients with SARS-CoV infection showed lymphocytic and monocyte infiltration, adrenal necrosis, and vasculitis of small veins of the adrenal medulla [22]. The antigens and genomic sequence of the SARS-CoV virus were isolated. There is no data on direct damage to the adrenal glands by the SARS-CoV-2 virus, but there is undoubtedly an indirect effect through acute stress, hypoxia, hypotension, sepsis and coagulopathy.

To date, there is no convincing evidence of a high risk of severe COVID-19 in patients with adrenal insufficiency, either primary (in patients with Addison's disease) or secondary (in patients with congenital adrenal dysfunction (CAD)). However, patients with Addison's disease and CAI have a higher risk of developing infectious diseases. Endocrinology societies recommend that patients with adrenal insufficiency follow the standard principles of doubling the dose of glucocorticoids taken for illness and fever and switching to intramuscular hydrocortisone injections for vomiting or diarrhea.

Thyroid

The thyroid gland (TG) is another endocrine gland whose function has been shown to change in both SARS and COVID-19 [23]. A study of autopsy results of patients with SARS-CoV infection showed apoptosis of follicular and parafollicular thyroid cells and desquamation of the follicular epithelium. However, neither viral RNA fragments nor antigens were isolated.

A retrospective study of 50 patients with COVID-19 showed that 64% of them had changes in thyroid hormones: 34% had isolated suppression of TSH production, 8% had a decrease in free thyroid hormones, 22% had TSH and free thyroid hormones [24]. Moreover, the degree of TSH damage correlated with the severity of COVID-19. The reasons for low TSH levels may be euthyroid pathology syndrome, glucocorticoid use, increased levels of pro-inflammatory cytokines and “cytokine storm”; The potential direct impact of SARS-CoV-2 on the hypothalamic-pituitary-thyroid axis is also discussed.

In the THYRCOV study, which included 287 patients with COVID-19, hypothyroidism was detected in 5.2%, and thyrotoxicosis in 20.2% of cases, among which 42.5% of cases were manifest thyrotoxicosis [25].

Cases of subacute thyroiditis have been described in patients with COVID-19 with a typical clinical picture and manifestation within 5–30 days from the onset of the disease, while it is possible that the widespread use of glucocorticoids in COVID-19 may mask a number of other cases of destructive thyroiditis. Subacute thyroiditis was most often associated with mild COVID-19 [16, 30,31].

Reproductive system

Analysis of the ACE-2 expression profile in various tissues showed a high level of expression in the testes, mainly on Leydig and Sertoli cells, which formed the basis for the theory of damage to the male reproductive system in COVID-19.

In a study by Song et al. [32], which included 12 samples of seminal fluid and 19 samples of testicular punctate, no RNA of the SARS-CoV-2 virus was detected in patients with COVID-19. However, autopsy data from patients with both SARS-CoV and SARS-CoV-2 revealed signs of orchitis with leukocyte infiltration, destruction, decreased sperm count in the seminiferous tubules, and thickening of the basement membrane. Another study [33] noted an increase in LH and prolactin levels with normal testosterone levels in patients with COVID-19 [34]

To date, there is no evidence of direct damage to testicular tissues by the SARS-CoV-2 virus; an alternative theory is immune-mediated, or inflammatory, damage to the testicles. Prolonged febrile fever leads to an increase in the temperature of testicular tissues, for which the optimal temperature is less than 37 ° C, promoting degeneration and destruction of germ cells and a decrease in spermatogenesis. The latter may also be affected by commonly used glucocorticoid therapy [32].

Conclusion

Thus, the accumulated clinical and scientific experience has shown an undoubted association of more serious outcomes of coronavirus infection with diabetes, obesity and hypertension. However, data on the expression of ACE-2 in endocrine tissues do not yet allow us to draw an unambiguous conclusion about the direct effect of the SARS-CoV-2 virus on the risk of developing extrapulmonary complications. However, central hypocortisolism and hypothyroidism are common endocrine complications of coronavirus infections. These changes are usually transient, more often developing during the disease, however, for hypocortisolism, a delayed manifestation is described several months after recovery. It is important to note that timely diagnosis and therapy can improve disease outcomes. Prospective observational studies are needed to assess the risk of reproductive disorders in patients.

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