
Glucocorticoids for COVID-19

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Abstract: The COVID-19 pandemic has affected every area of healthcare in every country in the world. The wide range of effects of the virus on all systems of the human body leads to a number of difficulties in the treatment of the disease. This article is a literature review that collects recommendations for the use of insulin in patients with COVID -19 taking glucocorticosteroids.

Keywords: COVID-19, diabetes, glucocorticosteroids, insulin, basal bolus therapy.

Introduction

COVID-19 was first reported in China in Wuhan in December 2019. As of March 1, 2021, the World Health Organization's COVID-19 dashboard had over 129 million confirmed cases of COVID-19 worldwide, including over 2.8 million deaths and over 104 million recoveries (WHO). SARS-CoV-2 is an RNA virus that can mutate. In human cells, the main entry receptor for SARS-CoV-2 is angiotensin -converting enzyme 2 (ACE2), which is highly expressed in lung alveolar cells, cardiomyocytes, vascular endothelium, and various other cell types [1]. In patients who died from complications of corona virus infection, a pathoanatomical autopsy revealed diffuse alveolar damage and infiltration of inflammatory cells with the formation of hyaline membranes in the lungs, myocardial inflammation, infiltration of liver lymphocytes, accumulation of macrophages in the brain, axonal damage, microthrombi in the glomeruli, and focal pancreatitis [2]. These data once again confirm that an acute inflammatory process occurs in the body. A retrospective study of 317 patients with laboratory-confirmed COVID-19 showed active inflammatory reactions (increased levels of interleukin-6, IL-6, and lactate dehydrogenase) within 24 hours of hospitalization, which correlated with the severity of the disease [3]. In addition, blood levels of IL-6 and lactate dehydrogenase are independent predictors of COVID-19 severity. The level of IL-6, which has pro- inflammatory properties, correlates with both the severity of the disease and coagulation parameters. IL-6, causing oxidative stress in the body, has a damaging effect, and this effect can lead to the rapid progression of metabolic disorders in COVID-19 [4]. In addition, increases in inflammatory markers such as D- dimer, ferritin, procalcitonin, CRP (C-reactive protein), and ESR (erythrocyte sedimentation rate) have been observed with COVID-19, which may increase the risk of microvascular and macrovascular complications arising from injury. endothelium [3].

Main part. It is known that any viral infection, including coronavirus, affects the human body at the cellular level and has a cytotoxic effect. As a result of this effect, inflammation factors (cytokines) are released in the body, which is a trigger of the autoimmune process [5]. Therefore, the use of glucocorticoids in severe forms of COVID-19 is quite pathogenetically justified. The randomized controlled trial (RCT) RECOVERY demonstrated that dexamethasone (6 mg daily for 10 days) in hospitalized patients with COVID-19 reduced 28-day mortality (odds ratio (OR) 0.83; 95% confidence interval [CI] 0.75-0.93), the duration of hospitalization and the need to switch to mechanical ventilation. prospective a meta-analysis of 7 RCTs further supported the benefit of corticosteroid therapy in reducing mortality in

critically ill patients with COVID-19 (pooled OR 0.66, 95% CI, 0.53-0.82) [6]. Thus, corticosteroid therapy is effective in severe COVID-19 [7]. It aims to support the central regulatory function of the activated glucocorticoid receptor α (GC-GR α). The greater the expression of glucocorticoid receptors in myeloid cells of bronchoalveolar lavage, the less pronounced neutrophilic pneumonia, an increase in the level of neutrophils, and the severity of symptoms. Translational research in patients with ARDS (acute respiratory distress syndrome), randomized to the use of methylprednisolone, showed the restoration of cellular concentrations and function of activated GC-GR α during glucocorticoid therapy, which leads to suppression of the activity of markers of inflammation, coagulation and proliferation of fibrocytes [6]. According to the recommendations of the Chinese Thoracic Society, short-course, low- and medium-dose glucocorticoid therapy [8] in critically ill COVID-19 patients improves outcomes but increases the risk of hyperglycemia. Low-dose dexamethasone has also been shown to reduce mortality in hospitalized patients with COVID-19 who require respiratory support [9]. Several retrospective studies have focused on carbohydrate metabolism disorders during the COVID-19 pandemic. One study included 39 patients without diabetes and no history of steroid therapy who were hospitalized for laboratory-confirmed coronavirus pneumonia. Twenty of these patients (51%) had hyperglycemia that persisted throughout the hospital stay. The level of glycemia returned to normal by the end of treatment. Given the mechanism of action of steroidal anti-inflammatory drugs, it would be possible to explain the occurrence of hyperglycemia in COVID-associated pneumonia during glucocorticoid therapy precisely by the contra-insular mechanism of action of glucocorticoids [10]. However, with a coronavirus infection, all metabolic processes in the body are disrupted, including carbohydrate metabolism. Against the background of the inflammatory process, insulin resistance increases, metabolic disorders occur, which is further enhanced during a cytokine storm. In human monocytes, elevated glucose directly increases SARS-CoV-2 replication, and glycolysis supports SARS-CoV-2 replication through production of mitochondrial reactive oxygen species and activation of hypoxia-induced factor 1 α . Therefore, hyperglycemia may contribute to the spread of the virus. In line with this, it has been suggested that hyperglycemia is an independent predictor of morbidity and mortality in patients with SARS [11]. Hyperglycemia is associated with worse prognosis of COVID-19 and is an independent predictor of severe disease [12]. Clinical guidelines recommend maintaining fasting glucose levels of 7.8–10 mmol /L for critically ill patients and a more stringent target of 4.4–6.1 mmol /L for patients with mild COVID-19 without significant hypoglycemia [13, 14, 15]. In addition, the direct cytotoxic effect of SARSCoV-2 on pancreatic β -cells, hepatocytes, myocytes, etc. should be taken into account. Damage to β -cells is the direct cause of the onset of insulin deficiency, a decrease in the level of one's own insulin and, as a result, hyperglycemia. Damage to hepatocytes and myocytes leads to increased insulin resistance [16]. Xiao et al . reported that of 95 patients with SARS treated with glucocorticoids at the maximum therapeutic dose, 34.7% of patients developed steroid-induced diabetes, and the maximum daily dose of methylprednisolone was the only predictor of diabetes [24]. In most patients, fasting glycemia returned to normal values after appropriate insulin therapy and after discontinuation of glucocorticoid therapy [17]. Correction of hyperglycemia during glucocorticoid therapy . In general, the starting dose of insulin therapy for hyperglycemia, identified for the first time against the background of the use of glucocorticoids for respiratory diseases, according to the recommendations of different authors, ranges from 0.3 to 0.5 U/kg per day (Table 1).

Recommended dose of insulin depending on the dose and glucocorticoid preparation used in the treatment of COVID-19 [4]

Methyl - prednisolone, mg / day	Prednisone, mg/ day	Dexamethasone mg/ day	Hydrocortisone, mg/ day	Total dose of insulin, U/kg body weight/day
≥32	>40	≥8	≥200	0.4
24	thirty	6	150	0.3
sixteen	20	4	100	0.2
eight	ten	2	fifty	0.1

The therapy regimen is basis- bolus [18]. Authors from Slovenia [19] published a paper in February 2021 in which they presented the results of a retrospective observation of patients with pneumonia and steroid -induced hyperglycemia detected in a hospital. Glycemic control was carried out 4 times a day (before main meals and at bedtime). Based on the experience of Indian colleagues, the authors recommend using repaglinide for fasting glycemia and before meals from 7.0 to 11.1 mmol /l and at bedtime above 11.1 mmol /l, with glycemia above 11.1 mmol /l when at least 2 measurements during the day, the authors recommend starting insulin therapy according to the basal bolus regimen, with the dose of insulin depending on the dose of glucocorticoids received [20]. At the same time, 60% of the daily dose is given to basal insulin, 40% to ultrashort insulin in a ratio of 2:2:1 before breakfast, lunch and dinner. The authors recommend titrating the dose of insulin every 2-3 days by 20% with persistent hyperglycemia above 11.1 mmol / l. Indian authors, when choosing the starting dose of insulin therapy, are guided by the level of glycated hemoglobin. With HbA1c between 6.5 and 8.5%, the recommended starting dose is 0.4 U/kg (50% of the daily dose was assigned to extended insulin) with a corrective injection when using a glucocorticoid . With HbA1c above 8.5%, the daily dose of insulin at the start is calculated as 0.5 U/kg, also with a corrective injection during the use of glucocorticoids [20]. The peak of hyperglycemia during methylprednisolone therapy is observed after 4-6 hours. Therefore, to correct hyperglycemia during the administration of methylprednisolone, it is better to use NPH insulin, the action profile of which fully corresponds to the peak of hyperglycemia under the influence of methylprednisolone [21, 22, 23]. The glycemic effect of dexamethasone, which can last up to 48 hours, is best compensated for with a long-acting analog insulin (glargine or insulin detemir), which has a hypoglycemic effect for more than 24 hours [24, 25, 26, 27]. In this case, an additional injection of insulin is carried out simultaneously with the introduction of the glucocorticoid preparation. Thus, when treating COVID-19 with systemic corticosteroids, due to the high likelihood of hyperglycemia, it is necessary to intensify glycemic control and carry out its correction by choosing an insulin preparation in accordance with the profile of a particular systemic glucocorticosteroid[2]

Conclusions : - Under the influence of the cytotoxic effect of the SARS-CoV-2 virus in the body of patients, the immune system fails, destruction of pancreatic β -cells and activation of the inflammatory process, which lead to disruption of homeostasis and metabolic disorders, including carbohydrate metabolism. – Hyperglycemia is an independent predictor of increased risk of hospitalization and severe disease in patients with COVID-19. - Against the background of taking glucocorticoids, the risk of manifestation of diabetes mellitus, decompensation of the glycemic profile, as well as the occurrence of transient hyperglycemia increases. – Control and correction of glycemia, taking into account the action profile of a specific glucocorticoid, with an appropriate insulin preparation, provides an improvement in the glycemic profile and, accordingly, the outcomes of COVID-19.

Literature

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