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Review

Anti-Diabetic Therapy in Covid-19

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Abstract

The COVID-19 virus is one of the most significant challenges of humanity and is causing thousands of deaths worldwide. Drugs active against the virus are being developed and tested, but it appears that lung lesions are the lethal ones that lead to the patient's death. The experimentation of new drugs has led to a few positive results, but an effective vaccine will soon become available, as the virus is further studied. People with chronic conditions, such as diabetes, are critically ill, and ongoing therapies can lead to management difficulties with many subsequent clinical complications in the pandemic period. Glycemic control and appropriate measures for a diabetic patient are key priorities, especially in patients that tested positive for COVID-19. This article describes the current evidence in the literature regarding the risks of the possible administration of antidiabetic drugs in the COVID-19 patient, as well as analyzing the blood glucose data and its homeostasis, which are fundamental data to combat a viral infection.

Keywords: COVID-19, inflammatory, diabetes, hyperglycemia, immunomodulators, Sars-Cov-2.

Introduction

Sars-Cov-2 infection

The COVID-19 infection, a new type 2 coronavirus, started its activity in China in late 2019 and has spread worldwide in a few months. At the time of writing this report, about 9.7 million infection cases, and 493.000 deaths were confirmed in more than 250 countries [1]. COVID-19 infection has a few stages with increasing gravity: the first is a mild asymptomatic form, while the second and third are characterized by a hyperactive inflammatory state and are serious stages that can lead to the person's death. The storm of cytokines that is generated quickly creates severe lung lesions with breathing difficulties and a generalized fibrotic state. Patients with chronic conditions such as diabetes are at risk of becoming more infected with further associated complications that make clinical management difficult. Drug treatment is based on ongoing antidiabetic treatments and the combination of anti-COVID-19 drugs. To date, the only direct antiviral being approved is Remdesivir [2].

Clinical management of the positive Covid-19 diabetic patient

Constant blood glucose monitoring is a crucial aspect to follow during an ongoing positive COVID-19 infection. All current guidelines recommend continuing the intake of antidiabetic therapies because there is no evidence that drugs used to fight diabetes can increase the risk of infection. Even after COVID-19 infection, glycemic control and continuation of standard ongoing therapies must be continued. However, this must be accompanied by the possibility that an infected patient needs to change the therapeutic dosage until it is even suspended in cases of critical states. Each case should be carefully evaluated, and individual therapy is the best solution by evaluating the contiguous clinical conditions. The normalization of blood glucose must always be kept in mind as a fundamental aspect not to be lost sight of to avoid hypoglycemia/hyperglycemia phenomena, as well as possible interactions between antidiabetic and anti-infective drugs. If diabetic therapy is not carefully monitored, the possible COVID-19 infection can generate severe complications.

Metformin is the drug most used in diabetic patients and is excreted by the kidneys. For this reason, in the event of an ongoing infection, kidney injury could lead to metabolic acidosis, typical in the case of this drug if its plasma concentration increases [3]. The most commonly used antivirals for COVID-19 are inhibitory drugs of the organic cation transporter (OCT), and metformin, which is its substrate, and these could produce a reduction in metabolization with consequent lactic acidosis. People with a severe hemodynamic situation should discontinue glucagon-like peptide-1 (GLP-1)drugs because they can lead to renal and gastrointestinal dysfunction with delays in gastric emptying and malabsorption of antivirals such as remdesivir and darunavir used to combat COVID-19 [4]. Besides, GLP-1 drugs lead to diarrhea with electrolyte loss and increased risk of arrhythmias in an infected patient.

Dipeptidyl peptidase-4 (DPP4) inhibitors are safe drugs for the kidney and give a little risk of hypoglycemia and should, therefore, be the most widely used drugs in the case of a positive COVID-19 infection in progress [5]. The use of sodium-glucose cotransporter-2 (SGLT-2) inhibitors leads to a very high risk of diabetic ketoacidosis in the case of infection [6]. The patients who have high quantities of ketone bodies and renal dysfunction should discontinue the SGLT-2 treatment. Infected patients taking sulphonylurea class drugs should consider new insulin therapy to avoid the risk of elevated hypoglycemia in patients with COVID-19 infection. Chloroquine, one of the antiviral drugs used against Covid-19, can also lead to a high risk of hypoglycemia, and this can cause severe complications. Obviously, this aspect is exacerbated if the considered patient also has renal complications [7]. The use of thiazolidinediones leads to the risk of water retention with edema in a hemodynamically unstable patient.

On the one hand, the use of antidiabetic drugs has led to an increased risk of infection and complications due to COVID-19 infection; on the other hand, there is also evidence of the usefulness of these therapies in case of infection. This is because it is now known that the most severe phase of infection is characterized by an uncontrolled hyperinflammatory phase with fatal lung lesions. The use of metformin has proven to be useful in reducing all the proinflammatory factors that characterize the COVID-19 infection, even if it is not clear what the mechanism of action of this phenomenon is [8, 9].

Also, DPP4 inhibitor drugs are studied in positive COVID-19 patients because DPP4 protein is present in alveolar cells, epithelial and inflammatory cells. The Middle East respiratory syndrome coronavirus (MERS-CoV) penetrates host cells using DPP4 [10]. However, it is not known if COVID-19 does the same upstream of the process that leads to the exploitation of the Angiotensin-converting enzyme 2 (ACE-2). If this is true, then the use of DPP4 inhibitors increases the risk of COVID-19 infection, but as for now, there are still no clinical data supporting this thesis [11]. The reduction of inflammatory markers is also known for GLP-1 drugs, and they have shown benefits in the presence of lung injury [12]. Some clinical data are beginning to demonstrate the truth of these hypotheses but at the moment, the state of the art regarding these issues is still in an embryonic phase.

Conclusions

The COVID-19 pandemic is generating deaths and infections worldwide, and drugs to counter its advance have been developing in recent months but without significant clinical results. The diabetic patient with an ongoing infection is a complex patient who requires careful clinical management since the risks are very high. Moreover, antidiabetic therapy cannot be suspended, and glycemic normalization must always be sought clinically. For a variety of circumstances, antidiabetic drugs represent an additional danger with severe complications if there is no careful clinical monitoring. However, there are few drugs that could have a certain positive activity in case of infection but currently there are no reliable data that prove the benefits of these therapies.

Conflict of Interest

The authors declare that there is no conflict of interest.

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