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Review Article

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DRUGS AND DIABETICS AFFECTED BY SARS COV-2

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Text

Since the outbreak of COVID-19, diabetes has been considered one of the susceptibility factors to infection.

Several studies have found a high prevalence of diabetes in patients with SARS-Cov-2 infection and have concluded that the incidence of diabetes, is a determinant of the severity and mortality of Acute Respiratory Distress Syndrome caused by depressed innate and humoral immune functions.

Moreover, previous viral pandemics have approved the link between diabetes and an increased morbidity and mortality rate, particularly during the outbreak of Severe Acute Respiratory Syndrome (SARS-CoV), followed by the emergence of influenza A (H1N1) in 2009, and also during the Middle East Respiratory Syndrome Coronavirus (MERS) infection in 2012.

Diabetes and COVID-19

In a recent published article, the authors reported that type 2 diabetics with an unfavorable progression appeared to share a common prescription for angiotensin converting enzyme inhibitors (ACE inhibitors) or angiotensin II receptor antagonists (ARB-II), based on their characteristics. ACE inhibitors are commonly prescribed in hypertensive diabetics or diabetic nephropathy, with cardioprotective and/or nephroprotective use to reduce the associated co-morbidities or vascular complications of diabetes.

The hypothesis that type 2 diabetics are more susceptible to SARS-CoV-2 contamination is related to the fact that it infects human cells via receptors that are precisely those of the angiotensin converting enzyme 2 (ACE 2). These receptors are located on the surface of lung epithelial cells as well as in the digestive tract, kidney, blood vessels, fatty tissue, etc., which explains the extent of the symptoms of the infection, not just respiratory. These same receptors are over-expressed in diabetic patients treated with ARA2 or ACE inhibitors, and obviously in cases of associated obesity, given that the renin angiotensin system regulates adipogenesis. Thus, these patients are more susceptible to the development of a severe SARS CoV2 infetion. As a result, these patients should be considered vulnerable and require special monitoring and more sustained sensitization, without any change in their previous therapies that may dysregulate their angiotensin-containing renin system.

Another hypothesis proposed by a team of Harvard University explain the increased susceptibility of type 2 diabetics, linked to the elevation of their glycated hemoglobin, which seems to interfere with heme and iron.

Anti-diabetic drugs and COVID-19

Currently, there are no data concerning the effects of anti-diabetic drugs on disease progression in COVID-19. For metformin, diabetic patients with chronic obstructive pulmonary disease, a protective role against pneumonia has been demonstrated. This may not be a coincidence since metformin is merely a derivative of chloroquine that was initially synthesized for use against malaria.

Since chloroquine and its derivatives also have a hypoglycemic effect, an association with metformin, or with sulfonamides or glinides, increases the risk of hypoglycemia.

Whereas for incretin-based therapy, experimental studies suggest that liraglutide, a GLP-1 receptor agonist, increases the expression of ACE2 receptors in the lungs of rats. These results in the current context of the COVID-19 and their relationship to anti-diabetic drugs is not yet fully elucidated, but remains a hypothesis that they increase the risk of altering the prognosis of these patients by overexpressing SARS CoV2. Concerning gliptins, studies in diabetic patients had noted that sitagliptin reduced the levels of pro-inflammatory markers such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). The Dipeptidyl peptidase-4 inhibitor could, via this effect, be involved in the SARS CoV2 infection or in the occurrence of its complications.

A study has been conducted to analyze the WHO database 'VIGIBASE', which includes all the undesirable effects reported using oral antidiabetic drugs. The study compared the occurrence of infections (106,469 infections) to other adverse events (305,415 adverse events) based on the drugs taken by patients at the time of each infection or side effect. These were pneumonia in 11.8% of cases, nasopharyngitis in 10.1% of cases, urinary tract infections in 6.2% of cases, sinusitis in 5% of cases, bronchitis in 4.8% of cases, and other infections in 5.5% of cases.

Analysis of Oral Anti-Diabetic prescribed in diabetics who had developed an upper respiratory infection showed an increase in risk in those on a Dipeptidyl peptidase-4 inhibitor. However, a meta-analysis conducted after the WHO findings, including 74 clinical trials of more than 12 weeks duration, concluded that there was no increase in the overall risk of infection with Dipeptidyl peptidase-4 inhibitor without specifying those of respiratory infections.

The COVID-19 therapeutic protocol and diabetes

Patients treated with chloroquine and hydroxychloroquine should be informed of the risks of severe hypoglycemia and associated symptoms. Blood glucose levels should be controlled and, if necessary, the treatment of diabetes may be adjusted in response to clinical symptoms suggestive of hypoglycemia during treatment.

Patients treated with lopinavir/ritonavir should be informed of the risks of decompensation of type 2 diabetes. Hyperglycemia has been reported in patients treated with protease inhibitors and has been severe and associated with ketoacidosis.

CONCLUSION

Several learned medical societies recommend discontinuing non-insulin treatments for type 2 diabetes and using insulin therapy as an alternative for better glycemic control. Likewise, insulin-therapy shouldn't be recommended in type 1 diabetic patients, exposed at an increased risk of ketoacidosis.

Rigorous glycemia monitoring is recommended when chloroquine or hydroxychloroquine and anti-diabetic agents are co-administered. A reduction in the dose of the antidiabetic agent may be necessary following reports of severe hypoglycemia in patients treated concomitantly with chloroquine or hydroxychloroquine and an antidiabetic agent. Monitoring of blood glucose levels is recommended and if necessary, treatment should be adjusted if hyperglycemia occurs during Lopinavir/Ritonavir therapy. ACE inhibitors or ARBs should not be discontinued due to SARS CoV2 infection unless the hemodynamic situation is precarious, in which case-by-case adjustment is recommended.

CONFLICT OF INTEREST

The authors declares that there is no conflict of interest.

AUTHORS' CONTRIBUTION

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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ETHICS STATEMENT

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