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THE IMPACT OF ANTIDIABETES AGENTS IN COVID-19 PATIENT

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ABSTRACT

Beckgroung:The current Covid 19 infection has been one of the most difficult challenges the world has faced in recent years, mainly due to fatal lung injury caused by a generalized inflammatory state.

Objective: Diabetes patients are those most at risk of contracting Covid infection19.

Materials and method: the main risk factors are age, concomitant drug therapy, kidney failure, hyperglycaemia, and copresence of cardiovascular disease. Regulating the blood glucose level is important.

Results: the patient with diabetes must be monitored both in the pharmacological treatment in case of infection and in the preventive phase in the regulation of glycaemia.

Conclusion: this article is intended to check the clinical condition of a diabetic patient with Covid19.

KEYWORDS: COVID-19, inflammatory, diabetes, hyperglycemia, immunomodulants, Sars-Cov-2.

INTRODUCTION

Sars-Cov-2 infection

The first outbreak of Covid19 was in Wuhan in China in December 2019. The symptomatic picture is mainly characterized by exhaustion, nausea, up to the most severe cases by lung complications that can lead to breathing difficulties. In the most severe conditions, a hyperinflammatory state is observed with a cytokine storm responsible for multiorgan dysfunction, which can lead to death. [2]

The diabetic patient

Diabetic patients have an immune system compromised by metabolic pathology characterized by a decrease in the activity of neutrophils and T lymphocytes and by the lack of an effective humoral immune response, which makes the patient with diabetes at high risk of viral or bacterial infection, especially in the airways.[3],[4] In diabetics, there is an increased risk of COVID-19 infection and increased mortality. the diabetic patient must be monitored.In the most serious conditions of a diabetic patient with Covid19 For patients with diabetes with Covid 19 the drug therapy with glyptin, incretin mimetics or SGLT2 inhibitors, the axis inhibitors / ARB antihypertensives, remains unchanged unless contraindications. In MERS itself, diabetes was considered a risk factor and a cause of serious complications.[5],[6] Likewise, among patients with influenza A (H1N1) in 2009, diabetes increased the risk of complications.[7]

The risk factors

The main predisposing risk factors are mainly secondary diseases caused by diabetes, such as coagulation dysfunction, generalized hyperinflammatory state, nephropathy, cardiovascular diseases characterized by thrombosis and lung lesions, immunosuppressed state. Elevated glucose levels are in patients with Covid 19 and are indicative of infection. The membrane glycoprotein ACE-2 a is useful in the penetration phase of the virus as Sars-Cov also binds ACE-2 in the pancreatic islets, causing functional damage and a reduction in insulin production.[11]

Clinical pharmacological aspects in the management of the diabetic patient during the COVID-19 pandemic

Antidiabetes agents

The continuous control and monitoring of blood glucose is of fundamental importance for the diabetes patient, even more so during the COVID-19 pandemic. Patients with diabetes can safely continue to take routine drug

therapies, to date there is no evidence that any anti-diabetes therapeutic agent can increase the risk of COVID-19 infection. Even if the patient with diabetes is affected by Sars-Cov-2, one should continue to monitor blood sugar levels and take the usual drug therapy. Probably in case Sars-Cov-2 infection leads the patient into serious complications, possible changes in dosage or medication could be considered, but should always be considered on a case-by-case basis. Several factors, including blood glucose, hemodynamic stability, nutritional status, kidney function, risk of hypoglycemia and drug interactions should be carefully assessed. However, the most commonly used antidiabetes medications in therapy may need to be modified or even discontinued in specific cases. Metformin is among the most commonly used medications for type 2 diabetes and is predominantly eliminated renal, in a COVID-19 patient careful monitoring of renal function should be performed to avoid risk of lactic acidosis caused by increased drug concentrations. Hypoxia may also increase the risk of lactic acidosis.[12] In addition some antivirals used to fight COVID-19 are inhibitors of the organic cation transporter OCT, metformin is a substrate of this transporter, inhibiting OCT may increase metformin concentrations in plasma, careful monitoring should be carried out to avoid this interaction. Some NSAIDs that can be used in the COVID-19 patient may decrease renal function and increase plasma metformin concentration. However, glucocorticoids may increase blood glucose, in which case a change in metformin dose may be considered, although at present the use of glucocorticoids does not seem to be recommended in the COVID-19 patient. Metformin may be discontinued in hospitalised and seriously ill patients due to the risk of lactic acidosis. Agonist glucagon peptide-1 receptor therapy (GLP-1RA) should probably be temporarily discontinued in patients with hemodynamic instability (which impairs absorption from subcutaneous sites), renal dysfunction and gastrointestinal dysfunction. GLP-1RA may cause a slowdown in gastric emptying and may result in clinically significant reductions in the rate and degree of absorption of certain oral drugs administered simultaneously such as darunavir or remdesivir antivirals.[13] Common side effects of GLP-1RA include nausea, vomiting and diarrhoea, which in a COVID-19 patient with similar gastrointestinal symptoms may lead to electrolyte depletion, careful evaluation should be made, GLP-1RA are excreted predominantly renal, in a COVID-19 patient with renal dysfunction an increase in drug concentrations may occur. No particular interactions with anticoagulants such as LHMW or IL1 and 6 inhibitors are known.

Dipeptidil peptidase-4 (DPP4) inhibitors are associated with a low risk of hypoglycemia and are relatively safe in a wide range of renal functions, which is a strength in the COVID-19 patient. Although renal function is severely impaired, a dose modification of drugs in this class should be considered.[14] Another strength of these drugs is that there are no particular interactions with CYP inhibitors, and this is a very important aspect in a COVID-19 patient with diabetes, who is a complex patient and can use highly interacting drugs such as antivirals. Also, there are no particular interactions with anticoagulants. Probably the use of SGLT-2 inhibitors is more complex in the COVID-19 patient, due to the risk of diabetic ketoacidosis, which can lead to potentially fatal cases.[15] The clinical condition of the patient, the concentration of ketone bodies, hyperglycemia, renal function are aspects to be taken into account for a possible suspension of treatment with SGLT-2. In addition, this category of drugs data suggest that the primary route of metabolism in humans is uridine 5′-diphosphorus glucuronidation (UDP) glucuronyltransferase (UGT) 1A3, 1A8, 1A9 and 2B7, and they are also OCT substrates. Interaction with antivirals such as darunavir and remdesivir should be carefully considered. There are no particular interactions with LHMW or IL-1 and 6 inhibitors. Insulin use should be carefully monitored due to the risk of hypoglycemia, and a dose change should be considered if the patient is on glucocorticoid therapy. In addition, a possible hypoglycemic additive effect due to hydroxychloroquine should be carefully evaluated. In patients with COVID-19 on sulfoniluree therapy, a change to insulin therapy should be considered because of the risk of high hypoglycemia in patients with Sars-Cov-2 infection. Caution with sulfonylureas should also be exercised in consideration of chloroquine, due to the risk of hypoglycaemia with both and if renal dysfunction is present.[16]

Thiazolidinediones such as pioglitazone should be carefully questioned for use in the COVID-19 patient, as this class of drugs is contraindicated in patients with hemodynamic instability, liver or cardiac dysfunction, which may be present in a severe COVID-19 infection Currently, existing evidence suggests that insulin is used compared to agents such as sulfonylureas or thiazolidinediones. (Figure 1)

Metformin	*Lactic acidosis*
GLP-1RA	*Diarrhoea and electrolyte depletion*
DPP IV Inhibitors	*Not particular risks*
SGLT2 inhibitors	*Increased risk of ketoacidosis*
Sulfonylureas	*Risk of hypoglycaemia*
Pioglitazone	*Risk of fluid retention and oedema*
Insulin	*Risk of hypoglycaemia*

Figure 1: Main risks from antidiabetic agents in patients with COVID-19.

Therapeutic agents for comorbidities

The therapy of the diabetic patient is complex and should aim not only at controlling glycemic homeostasis but also at a series of comorbidities that can worsen the clinical picture. The medical antihypertensive therapy of choice for the diabetic patient involves the use of ACE inhibitors or angiotensin antagonists2. These drugs not only reduce blood pressure and proteinuria but also slow the progression of diabetic nephropathy. To date there are conflicting and as yet inconclusive results on their use in this period of the COVID-19 pandemic, causing an increase in the risk of infection that they could cause by raising ACE-2 concentrations. It remains to be emphasized that there is currently no clear evidence for or against the use of ACEI/ARB in people with diabetes at risk or infected with Sars-CoV-2.[17] Currently, most international organisations recommend the continuation of ACEI/ARB therapy, unless there are explicit contraindications such as uncontrolled kalaemia or renal stenosis.[18][19] Patients with diabetes undergoing treatment with antiaggregants such as 100mg acetylsalicylic acid should continue to take them. There is currently no evidence of a possible suspension unless there are clear contraindications such as a risk of gastrointestinal bleeding or severe renal impairment. However, in severe COVID-19 patients co-administration of acetylsalicylic acid and corticosteroids or acetylsalicylic acid and heparin may lead to an increased risk of ulcer and gastrointestinal bleeding. In addition, there is currently no direct evidence for statin suspension in patients with diabetes and COVID-19. However, it is of great importance to consider that if the viral infection leads to renal damage (e.g. creatinine clearance <60 ml/min) or liver damage with increased transaminases,[20-21] the statin concentration may increase causing a worsening of the clinical picture with risk of myopathy and liver damage. In addition, antiviral protease inhibitors such as lopinavir in association with statins should not be used because of drug interaction and the risk of increased statin concentrations.[22] Therefore for the use of statins we suggest individualized decision on a case by case basis.

Anti-diabetes agent as potential therapeutic treatment for COVID-19

Some therapeutic agents used to treat diabetes have shown evidence of effectiveness against Sars-Cov and MERS, epidemics similar to Sars-Cov-2. It is now known that in the most severe stages of COVID-19 infection an overactive and uncontrolled inflammatory host system caused by a cytokinic cascade is responsible for multi-organ dysfunction and serious fatal lung lesions. The use of metformin has shown a decrease in inflammatory markers in patients with Sars-Cov and MERS, however its use in the severe COVID-19 patient should be carefully assessed in view of the risks described above.[23][24] The use of DPP IV inhibitors (glyptine) is being studied in the COVID-19 patient. The DPP4 protein is expressed in many cells including alveolar epithelium and inflammatory cells. MERS-CoV uses DPP4 to enter host cells[25], but it is not known whether Sars-Cov-2 also uses the same protein to enter the cell, in addition to ACE-2. If this is demonstrated, the use of glyptins could decrease the risk of Sars-Cov-2 infection but this has not been demonstrated so far. The potential benefit in the treatment of Sars-Cov-2 infection with DPP IV inhibitors remains to be further investigated.[26] Similar to metformin, the effects of reducing inflammatory markers are also known for GLP-1RA and have also demonstrated a potential therapeutic benefit in acute lung lesions.[27] However, the available data are limited to experimental models and their benefit still remains to be studied.

CONCLUSIONS

The global pandemic from COVID-19 represents one of the greatest health challenges in human history. Pending the discovery of an effective vaccine and antivirals directed against Sars-Cov-2, it is essential to recognize factors that may increase the risk of infection or worsen complications from COVID-19. The identification of effective preventive and therapeutic strategies is urgently needed especially for patients with chronic diseases such as diabetes. Patients with diabetes are at greater risk in this pandemic period, and even diabetes therapy can be complex to manage during a COVID-19 infection. Clinical data and EBM to be translated into guidelines by scientific societies and countries are needed to better guide clinicians in the complex management of a diabetes patient who is COVID-19 positive.

Main statements

I, the undersigned, Francesco Ferrara and any other author, declare that:

· The manuscript was written entirely by the authors;

· All authors made an equal contribution in the development of the paper;

· We have no conflict of interest;

· We have not received funding/source;

· There are no sensitive data and no patients were recruited for this study;

· The document does not conflict with ethical legislation.

Regards

The authors

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