



Pharmacological management of COVID-19 in type 2 diabetes

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ABSTRACT

Evidence suggests that diabetes is one of the most relevant comorbidity in affecting the prognosis of COVID-19. Albeit there are no specific trials nor subgroup analysis showing the effect of COVID-19 therapies in patients with diabetes, selected features of this disease and the side effects associated with certain drugs require a proper knowledge to optimize the pharmacological therapy of patients with diabetes and COVID-19. While chronic anti-hypertensive and glucose-lowering therapies should not be discontinued nor preferred for preventive purposes, the low-grade pro-inflammatory, the thrombosis-prone status of diabetes, the role of acute hyperglycaemia in promoting adverse outcomes in patients admitted to ICU, and the observed increased mortality in patients with poor long-term glycaemic control delineate a delicate balance in case of severe forms of COVID-19. Here, we briefly summarized some of the key pharmacological issues linked to the management of patients with diabetes and COVID-19, in order to provide indications to minimize the deleterious effects of the concomitant presentation of these diseases and to use the existing pharmacological options in an appropriate manner.

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1. Introduction

Coronavirus disease (COVID)-19, the infectious disease caused by SARS-CoV-2, has spread all over the world. Diabetes has emerged as one of the most important comorbidities in affecting the prognosis of people with COVID-19.¹ Diabetes, and in particular type 2 diabetes, is characterized by a pervasive status of low-grade inflammation, the presence of multiple comorbidities, and a thrombosis-prone profile.^{2–5} These predispose patients with diabetes to develop a severe hyper-inflammatory reaction, coagulation abnormalities, and multi-organ failure, usually underlying the most severe forms of COVID-19.⁶ On the other side, some anti-inflammatory drugs, e.g. corticosteroids, are known to worsen glycaemic control in people with diabetes, a phenomenon that should be avoided in patients admitted to ICU.⁷ Hyperglycemia at hospital admission has been linked to an increased death rate in COVID-19 patients with and without diabetes.⁸ In addition, SARS-

CoV-2 infection *per se* has been suggested to promote and aggravate the diabetic condition, given the ability of the virus to promote both systemic acute inflammatory responses, likely causing insulin resistance, but also β -cells deterioration.⁴ These considerations delineate a delicate balance between the potential benefits and harms of pharmacological therapies in patients with the concomitant presentation of diabetes and COVID-19.

In this article, we synthesize key pharmacological aspects of the management of COVID-19 in patients with diabetes, focusing on both the chronic therapies, *i.e.* the anti-hypertensive and the glucose-lowering, and the drugs used for the management of patients in case of infection, *i.e.* the anti-inflammatory (hydroxychloroquine, corticosteroids, and the anti-cytokine biologicals), the antivirals, and the anti-coagulant ones.

2. Chronic therapies- antihypertensives and glucose-lowering therapies

Angiotensin-Converting-Enzyme-2 (ACE2) receptors have been identified as the receptors for the spike-protein of the “Severe acute respiratory syndrome coronavirus 2” (SARS-CoV-2).⁹ A serious concern, particularly for diabetes, about a possible induction of the ACE2 was suggested related to the use of ACEi or ARBs.^{10,11} Both ACEi and ARB are widely used for the treatment of hypertension and different kidney diseases, two conditions very often present in diabetes. Specific studies have later confirmed that these drugs are neutral or even somehow

Abbreviations: (ACE2), Angiotensin-Converting-Enzyme-2; (ARBs), Angiotensin-Receptor-Blockers; (ACEi), Angiotensin-Converting-Enzyme inhibitors; (COVID-19), Corona Virus Disease 2019; (DPP4 inhibitors), Dipeptidyl-peptidase 4 inhibitors; (GLP-1RA), Glucagon-Like-Peptide-1 Receptor Agonists; (ICU), Intensive Care Unit; (SARS-CoV-2), Severe acute respiratory syndrome coronavirus 2; (SGLT-2 inhibitors), Sodium-glucose-transporter-2 inhibitors.

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helpful during the COVID-19,^{12,13} thus suggesting that suspending such therapies has no benefit in preventing severe forms of COVID-19. This applies also to patients with diabetes.^{14,15} Rather, mechanistic hypotheses suggest that drug discontinuation in case of infection can eventually promote adverse outcomes through a detrimental effect on ACE1/ACE2 balance.¹⁶ On the contrary, an ongoing trial will test if introducing *de novo* an ACEi in case of infection can be helpful to attenuate COVID-19 outcomes (NCT04366050).

Inflammation plays a key role during the SARS-CoV-2 infection. The Dipeptidyl Peptidase 4 receptor (DPP4) is expressed ubiquitously in many tissues, including in the respiratory tract, where it cleaves a large range of protein substrates, including cytokines and chemokines.¹⁷ DPP4 was also suggested to be the functional receptor of other human coronaviruses, thus representing a potential target to reduce the severity of the COVID-19 by attenuation of both viral spreading and of the inflammatory response.^{17,18} DPP4 is the target of incretin-based therapies, and this opened the discussion whether DPP4-inhibitors, currently used for the treatment of people with type 2 diabetes, may be effective against SARS-CoV-2 infection.¹⁷ Recent data from observational studies have shown both a beneficial or a neutral effect of DPP-4 inhibitors on COVID-19 related mortality.^{15,19,20} Worth mentioning, a genetic variant within the gene encoding for DPP9, a serine protease of the same family of DPP4, is associated with severe forms of COVID-19,²¹ while diverse DPP4 inhibitors have different selectivity among various DPP, with divergent effects on immune cells activation.²² Two ongoing trials are exploring if DPP-4-inhibitor treatment on top of the insulin regimen can help to ameliorate the severity of the COVID-19 (NCT04341935; NCT04542213).

It has been hypothesized that the Sodium-Glucose-Transporter-2 inhibitors (SGLT-2i), the Glucagon-Like-Peptide-1 Receptor Agonists (GLP-1RAs), Pioglitazone and even Insulin might induce an over-expression of the ACE2, therefore increasing the risk for more serious consequences for people with diabetes if infected.²³ The alarm has not been justified; on the contrary all the above-mentioned drugs for the treatment of diabetes also show very good anti-inflammatory action and, in the case of GLP-1RAs and SGLT-2i, proven cardiovascular and renal protection.²⁴ Recent data from large observational cohorts showed a neutral effect in terms of COVID-19 related mortality in patients initiating such drugs,²⁰ while metformin and insulin users showed, respectively, a decreased and an increased COVID-19 related mortality.^{20,25} Whether these effects are drug-intrinsic or simply reflect the use of different drug classes at different stages of diabetes progression is matter of investigation.^{20,25,26} An ongoing trial is testing if the SGLT-2 inhibitor dapagliflozin is able to attenuate the progression of COVID-19 in patients with or without diabetes (NCT04350593). However, at present there are no data to justify a change in the glucose-lowering regimen for preventive purposes against COVID-19 in patients with diabetes, nor any drug should be added to the treatment schedule in case of infection. Also, ambulatory treatment should not be suspended in case of mild COVID-10.

3. Complications-hyperglycemia- impact and management & thrombosis

As reported above, diabetes is one of the most common comorbidities of severe COVID-19.¹ However, what is intriguingly emerging is that beyond diabetes itself and the long-term glycemic control, the level of hyperglycemia at the time of the hospital admission for COVID-19 is conditioning a worse prognosis.^{8,14,27-32} Hyperglycemia exposes at higher risk of complicated COVID-19, particularly in people without previous diabetes or with diabetes discovered at the hospitalization,³³ a condition being explored also to ascertain if COVID-19 itself can trigger the development of diabetes due to β -cells disruption.⁴ Furthermore, some studies also report that glucose variability, on top of the acute hyperglycemia, may have a damaging effect.^{8,32} These findings suggest that acute hyperglycemia, in addition to long-

term glycaemic control,³⁴ may play a key role in worsening the prognosis of people with COVID-19.³⁵ In addition, short-term glycemic control might improve the prognosis of patients with diabetes hospitalized for COVID-19,³⁰ albeit it cannot be firmly established whether acute hyperglycemia is an etiological factor driving poor prognosis or simply reflect disease severity. Of note, the deleterious effect of acute hyperglycemia in diabetes, more than the previous glycemic control, was previously shown in the Intensive Care Unit (ICU) setting, where an increased gap between admission glucose and HbA1c-derived average glucose levels has been demonstrated to be a predictor of mortality in critically ill patients with diabetes.⁷ The damaging impact of acute hyperglycemia and the effect of glucose variability were both already documented before the COVID pandemic.^{17,36,37} Moreover, it is also well known that acute hyperglycemia in the ICU is more dangerous for people without diabetes than for people with diabetes.³⁷

However, excluding some recommendations released by the experts in diabetes,³⁸⁻⁴⁰ in the available National and International professional guidelines and expert recommendations (⁴¹ accessed and examined through PubMed accessed on October 20 18th 2020) the problem of diabetes and, particularly of the need for a strict control of hyperglycemia, is neglected. Continuous glucose monitoring should be mandatory to ensure stable metabolic compensation. Patients in the ICU requiring therapy for glycemic control should be handled solely by intravenous insulin using exact dosing with a perfusion device,³⁸⁻⁴⁰ a recommendation deriving from historical trial showing a reduction in short-term morbidity and mortality in critically ill adults targeted to lower blood glucose levels with insulin, independently of the etiological factor promoting ICU admission and valid also for patients without diabetes.^{42,43}

Thrombosis emerged as one of the most important complication of COVID-19 and high dose anticoagulants treatment has been shown to be life-saving.⁴⁴⁻⁴⁷

Diabetes is characterized by a thrombosis-prone status.⁴⁸ Hyperglycemia is a pro-thrombotic factor by itself,^{2,49} and this is particularly true in the case of acute hyperglycemia^{2,49,50} or glucose variability.⁵¹ These aspects of diabetes were initially not taken into account in COVID-19 management.^{38,39} It is worth remembering that acute hyperglycemia induces an activation of coagulation also in people without diabetes.^{2,49,52} This phenomenon, which is driven by oxidative stress generation, is also accompanied by the induction of inflammation and endothelial dysfunction, which, together, may precipitate a cardiovascular event and promote other detrimental outcomes, particularly in the case of the COVID-19.³ Prophylactic anti-coagulant therapy should represent a routine approach to manage patients with diabetes and COVID-19.

4. Management of infection

4.1. Corticosteroids

The use of corticosteroids was not recommended at the beginning of the COVID-19 pandemic.⁵³⁻⁵⁵ This was also the official position of the WHO.⁵⁵ This recommendation was mainly driven by the previous experience with influenza, SARS-CoV-1, or MERS-CoV.⁵³

COVID-19 is characterized by an intense inflammatory reaction⁵⁶; therefore, corticosteroid treatment could have had an important role to suppress lung and other tissues inflammation. The recent publication of the RECOVERY Study shows that the use of Dexamethasone decreases mortality in people affected by severe forms of COVID-19,⁵⁷ albeit contradictory findings have also been reported.⁵⁸

On the other side, data seem to show that the use of corticosteroids in people with diabetes is accompanied by a worse prognosis.^{41,59} In the same studies, however, it is also confirmed the deleterious effect of hyperglycemia on the outcomes of the disease.^{41,59} A possible explanation is that the use of corticosteroids impacts on the levels of glycemia and that, probably, the advantages of using them may be lost because of the damage induced by hyperglycemia.⁶⁰ While definitive data

regarding the usefulness of using corticosteroids in patients with diabetes and COVID-19 are not available at present, this consideration further emphasizes the need of frequent glycemic monitoring and control in patients with diabetes and COVID-19, especially when corticosteroids therapy is introduced.

4.2. Hydroxychloroquine

Preliminary evidence suggested a potential benefit of using hydroxychloroquine in the COVID-19, until two publications suggested the uselessness of this treatment.⁶¹ The data of two papers were questioned for serious methodological issues revealed after their publication^{62,63} and the possible benefits of this treatment are still under research.⁶⁴ During this “debate” hydroxychloroquine use was still promoted by media. Reports of success in early clinical studies were widely publicized by news outlets, politicians and on social media.⁶⁵ However, hydroxychloroquine may have serious adverse effects, particularly for the heart.⁶⁶ It is well known that cardiovascular diseases very often accompany diabetes, so the use of hydroxychloroquine might have exposed people with diabetes at higher risk of complications. Moreover, hydroxychloroquine is increasing the risk of hypoglycemia,⁶⁷ which itself is a serious risk factor for cardiovascular complications.⁶⁸ Albeit no trial tested the effect of hydroxychloroquine specifically in patients with COVID-19 and diabetes, results from large trials showed no benefit in terms of reduced mortality and an increased incidence of serious adverse events in patients with COVID-19 treated with such drug.⁶⁹ Given the latest recommendations regarding hydroxychloroquine and COVID-19, this aspect should no longer represent a concern.

4.3. Remdesivir

Remdesivir is the only FDA approved anti-viral drug for the treatment of severe forms of COVID-19.⁷⁰ While the WHO-conducted trial showed no benefit in terms of survival in patients with COVID-19,⁷¹ another study showed a shortening in the time to recovery in hospitalized adults and a nonsignificant trend also for improved survival at day 29 from hospitalization.⁷² While the discussion regarding its benefit for COVID-19 management is far from being closed, remdesivir is being used in clinical practice in patients with severe forms of the disease. None of the two available studies^{71,72} showed data for the subgroup of patients with diabetes, precluding the exploration of its effect in this specific setting. However, remdesivir is known to promote liver and kidney damage.⁷⁰ Given the high prevalence of both liver, e.g. non-alcoholic fatty liver disease, and kidney, e.g. diabetic nephropathy, diseases in patients with diabetes, it is of utmost importance to evaluate the presence of these comorbidities and to monitor liver and kidney function when the therapy is introduced.

4.4. Ivermectin

Ivermectin is being prescribed as a potential treatment for COVID-19, especially in patients with mild forms of the disease. Previous pre-clinical work showed a potential glucose-lowering effect for ivermectin,⁷³ albeit no data substantiated such observation in humans. While there are no available data for ivermectin use in patients with diabetes and COVID-19, a recent trial showed no benefit for a 5-day course of ivermectin in patients with mild COVID-19, prompting the regulatory agencies to recommend against its routine use.^{74,75}

4.5. Anti-cytokines biologicals

COVID-19 patients, especially those experiencing the worst outcomes, are often accompanied by an overwhelming inflammatory reaction, usually referred to as “cytokine storm”.⁶ This phenomenon is further enhanced by pre-existing co-morbidities, as in the case of type 2 diabetes.⁷⁶ A number of trials are testing if targeting major cytokines

with existing anti-cytokine biologicals in COVID-19 patients provides benefit in terms of mortality or other outcomes.⁷⁷ Diffuse, rationale-based use of such drugs is being done in hospitalized patients with COVID-19.⁴ As mentioned above, diabetes, and especially type 2 diabetes, has a pervasive inflammatory component in its etiopathogenesis.^{5,76} Thus, it is not surprising that a number of anti-inflammatory drugs, including anti-cytokines biologicals, have showed a certain degree of glucose-lowering effect in both patients with and without diabetes,⁷⁸ as also substantiated by clinical trials.⁷⁹ In particular, this applies also to tocilizumab (anti-IL-6), anakinra (anti-IL-1 receptor), and multiple TNF- α inhibitors, i.e. frequently used drugs in patients with COVID-19.^{4,78} However, the magnitude of the glucose-lowering effect should not represent a concern relative to the risk of hypoglycemia.⁴ Rather, such drugs are expected to be particularly beneficial in severe COVID-19 patients with diabetes, as well as with other diseases characterized by low-grade inflammation.⁷⁶ However, no specific data relative to the effect of these drugs in the subgroup of patients with diabetes and COVID-19 are available, with the exception of epidemiological findings suggesting a decreased COVID-19-related mortality rate in subjects with diabetes and on treatment with TNF- α inhibitors prior to infection.²⁵

4.6. Convalescent plasma and monoclonal antibodies therapies

The use of plasma from convalescent patients was proposed from the beginning as a treatment to halt virus progression and limit the consequences of COVID-19, so the FDA authorized its use as an investigational drug in this context.⁸⁰ RCTs and other studies have provided contrasting results. As a result, three meta-analysis found a consistent benefit,⁸¹ a low-quality evidence for mortality reduction⁸² and no substantial benefit on a range of possible outcomes,⁸³ respectively. Type 2 diabetes is accompanied by a range of alterations relative to the immune system, which underlie a higher susceptibility to selected infections and a blunted antibody response to vaccination.⁸⁴ Thus, it might be hypothesized that patients with type 2 diabetes are among those benefitting most by convalescent plasma therapy. One small cohort study exploring the effect of convalescent plasma in patients with type 2 diabetes showed that, when compared to a matched cohort with similar clinical characteristics on conventional therapy, patients treated with convalescent plasma had a higher rate of discharge from the hospital, with only few and non-serious adverse events reported.⁸⁵ Given that the rationale underpinning the use of monoclonal antibodies is the same, similar results might be expected. At present, monoclonal antibodies have been tested only in patients with early and mild COVID-19, providing preliminary results in terms of reduction of viral load and subsequent rate of hospitalization.⁸⁶ No data are available specifically for patients with diabetes. However, this should not represent any contraindication for the use of such drugs.

5. Concluding remarks

People with diabetes are among those with an increased risk of death in case of COVID-19.¹ Myocardial injury is a very frequent complication of COVID-19, being more frequent in people with a previous cardiovascular disease.⁸⁷ This last condition is very often present in diabetes⁸⁸ and should justify a particular attention to this population. Very well-known risky situations in diabetes, such as the effect of acute hyperglycemia, the impact of corticosteroid therapy, the side effects of hydroxychloroquine as well as the specific thrombotic prone-status should be well acknowledged in presence of the COVID-19. Thus, the management of patients with diabetes and COVID-19 might be optimized by an increased recognition of the importance of both short and long-term, i.e. prior to infection, glucose control, thrombosis prevention, and the hypo- or hyperglycemic side effects of selected anti-inflammatory drugs. Rationale-based treatment algorithm and recommendations have been recently published^{4,36} and might be the best

strategy to manage patients with diabetes and COVID-19, until specific evidence regarding optimal therapy in this setting is available.

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Ethical statement

This is a narrative review and, as such, no raw data were generated.

CRedit authorship contribution statement

AC and FP made the literature search and wrote the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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