Review article

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Antidiabetic drugs in patients with Covid-19 infection

Konstantinos Theocharis[1], Christina Antza[1], Georgios Kostopoulos[2], Vasilios Kotsis[1]

[1]Hypertension Center, 3rd Department of Medicine, Papageorgiou Hospital, Aristotle University of Thessaloniki, Greece

[2]Department of Endocrinology, 424 Military Hospital of Thessaloniki, Greece

ABSTRACT

The COVID-19 pandemic has posed new challenges to the management of the ever-growing group of patients with Diabetes Mellitus (DM). An important question to be answered is which, if any, specific glucose-lowering therapy is associated with worse or better COVID-19 related outcomes for patients with DM. Physicians had to make such management decisions in the absence of robust scientific evidence so far. After nearly two years into the pandemic, there are now a fair number of published studies comparing the premorbid or in-hospital use of certain anti-diabetic medications and relating them to certain COVID-19 outcomes, and there are also a number of published recommendations for the management of people with DM during the pandemic. The purpose of this review is to examine the relationship between the different classes of antidiabetic medications and COVID-19 related outcomes, as well as to make evidence-based recommendations regarding the use of glucose-lowering therapies during acute COVID-19 infection.

KEY WORDS: *Diabetes, Type 2 Diabetes Mellitus, Antidiabetic agents, Covid-19, mortality, morbidity*

INTRODUCTION

The COVID-19 pandemic has undoubtedly created a new era in medicine, to which physicians had to be adapted in a short period of time. As of December 2021, the number of SARS-CoV-2 infections worldwide exceed 270 million[1]. The corresponding number in Europe is about 93 million, and in Greece the total cases so far have reached over a million[2,3]. The real number could actually be much higher (10-fold or more),since many infections go undiagnosed due to a lack of symptoms or due to low disease severity which does not prompt a timely viral test[4,5]. The Case Fatality Rate (deaths/confirmed cases) is 1,95%, while the Infection Fatality Rate (deaths/total cases) is estimated at 0,15-1,0%, although this number varies greatly depending on age and certain

Corresponding author:

Prof. Vasilios Kotsis, MD, PhD
3rd Department of Medicine,
Papageorgiou Hospital,
Aristotle University of Thessaloniki, Greece
E-mail: vkotsis@auth.gr
Tel.: +30 6974 748860

ABBREVIATIONS: *COVID-19: Coronavirus Disease 2019, SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2, US: United States, T2DM: Type 2 Diabetes Mellitus, PWD: People with Diabetes, OR: Odds Ratio , DPP4-i: Dipeptidyl-Peptidase 4 inhibitors, SGLT2-i: Sodium Glucose Transporter-2 inhibitors, GLP-1 RA: Glucagon-Like Peptide 1 Receptor Agonists, DARE-19: Dapagliflozin in Respiratory failure in patients with COVID-19, HR: Hazard Ratio, CI: Confidence Interval, AKI: Acute Kidney Injury, MALA: Metformin Associated Lactic Acidosis, UK: United Kingdom, ER: Emergency Room, DKA: Diabetic Ketoacidosis, GI: Gastrointestinal, CD26: Cluster of Differentiation 26, ACE2-R: Angiotensin-Converting Enzyme 2-Receptor, ICU: Intensive Care Unit, CORONADO: Coronavirus SARS-CoV-2 and Diabetes Outcomes, IL-6: Interleukin-6*

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comorbidities[6,7]. In the U.S. , COVID-19 is now the third leading cause of death after cardiovascular events and cancer[8].

On the other hand, Type 2 Diabetes Mellitus (T2DM) has also been characterized as a modern day "pandemic", with over 470 million people worldwide living with the disease[9]. In Europe, the number of people with T2DM is about 61 million, accounting for 9,2% of the adult population, with estimates that this percentage will rise to more than 13% by 2045[10]. Greece is in the 22th place of Europe, with 7,4% of the adult population living with T2DM. The vascular, cardiac, renal and other complications of diabetes have been well established, with the disease ranking 9th as a cause of death worldwide[11].

It has been observed early in the course of the pandemic that People with Diabetes (PWD) had an increased chance of having severe COVID-19 compared to non-diabetics, and also had a higher chance of being hospitalized or dying due to COVID-19[12-17]. The OR for severe COVID-19 or in-hospital death varied by study, but generally was between 2.0 and 3.0 for people with T2DM, compared to people without diabetes. The importance of adequate glycemic control has also been highlighted, since an elevated HbA1c% (>7,5%) has been correlated to an increased in-hospital mortality compared to lower values[13].

What is less well established, however, is the optimal care of PWD during the pandemic. There are a number of published studies (mostly observational ones), comparing the premorbid or in-hospital use of certain diabetes medications in order to identify possible COVID-19 related outcomes, such as need for hospitalization and death[18-27]. There are also several published recommendations regarding the management of PWD during the pandemic[28-35], but unfortunately the level of disagreement is high, creating confusion regarding the best management options. Hence, the aim of this review was to investigate the literature and provide evidence for the use of antidiabetic medications in patients infected with COVID-19, hopefully shedding light onto this tangled topic.

EVIDENCE FOR THE USE OF SPECIFIC CLASSES OF DIABETES MEDICATIONS

Most studies so far have compared the premorbid (and less frequently, the in-hospital) use of metformin, dipeptidyl-peptidase 4 inhibitors (DPP4-i), sodium glucose transporter-2 inhibitors (SGLT2-i), glucagon-like peptide-1 receptor agonists (GLP-1 RA), sulfonylureas, thiazolidinediones and insulin regarding different mortality and morbidity outcomes for PWD and SARS-CoV-2. It should be noted, however, that most of the studies are observational (with the exception of the DARE-19 trial[23]) and the results should be treated with caution, as it is likely that confounders have played an important role.

METFORMIN

Many studies have shown that the premorbid use of metformin is associated with a decreased COVID-19 related mortality, compared to no metformin[18,22,24,26]. The largest one, a nationwide observational study in England with over 2.800.000 participants and 13.500 COVID-19 deaths, demonstrated a hazard ratio (HR) of 0·77 (95% CI 0·73-0·81) for metformin versus no metformin, regarding COVID-19 related death[18]. Data from the US have shown a decreased in-hospital COVID-19 related mortality with the premorbid use of metformin, but only in women (HR 0·785, 95% CI 0·650-0·951)[26]. Contrasting these outcomes is the SEMI-COVID study, which showed no reduced mortality with metformin use after propensity matching[21]. However, the sample size was much smaller compared to the other studies, rising queries about the statistical strength. There is also a published meta-analysis of five studies comparing the preadmission use of metformin with no metformin use, where the pooled analysis revealed significantly reduced odds for mortality with the use of metformin (pooled odds ratio [OR] = 0.62; 95% CI: 0.43–0.89)[24]. Overall, the premorbid use of metformin seems to be predictive of better outcomes and reduced mortality for PWD and COVID-19, compared to no metformin. One possible explanation for this includes the anti-inflammatory effects of metformin on the endothelium[36,37], which may dampen the systemic inflammation and cytokine storm provoked by SARS-CoV-2. It is possible, however, that these results are affected by confounders, since PWD on metformin are more likely to be younger and earlier in the course of T2DM.

Regarding the use of metformin during acute COVID-19, it should generally be withdrawn when the illness is severe or critical[28-35]. Hypoxia, haemodynamic instability and acute kidney injury (AKI) secondary to dehydration can all significantly increase the chance of lactic acidosis[38]. Metformin-associated lactic acidosis (MALA) is a very serious condition, with reported mortality rates of 30-50%[38]. When it comes to mild or moderate disease, opinions start to diverge, with some advocating for discontinuation of metformin with any level of illness[28,34], and others recommending that it is continued[29,30,35]. The Hellenic Diabetes Association recommends that metformin is discontinued during acute illness, especially in patients with concurrent dehydration[39].

SODIUM-GLUCOSE TRANSPORTER -2 INHIBITORS (SGLT2-I)

This widely used class of anti-diabetic medications has also shown a benefit for PWD and COVID-19. According to the UK Cohort study, the premorbid use of SGLT-2i was associated with a HR of 0·82 (95% CI 0·74-0·91), compared

to no SGLT-2i use, regarding COVID-19 related death[18]. A different study (N3C) compared the premorbid use of SGLT-2i to the use of DPP-4i and found lower rates of 60-day mortality (OR 0.66 [95% CI 0.50-0.86]), Emergency Room (ER) visits and hospitalization with SGLT-2i use[19]. DARE-19 (DApagliflozin in REspiratory failure in patients with COVID-19), a multicenter, randomized, double-blind, placebo-controlled study involving 1.250 participants, compared the use of dapagliflozin (10 mg once daily for 30 days) to matching placebo for patients with COVID-19 requiring hospitalization, that had at least one cardiometabolic risk factor, such as T2DM or cardiovascular disease. Regarding the primary outcomes of the study, there was no significant difference between the two groups, but there was a trend towards reduced mortality and organ failure in the dapagliflozin group. This study also demonstrated the absence of a safety signal, since both groups had the same frequency of serious adverse events[23].

Most published recommendations still suggest that the discontinuation of SGLT-2i in hospitalized patients with COVID-19 is preferred due to the risk of dehydration, AKI, and Diabetic Ketoacidosis (DKA)[28-35]. However, the results of the DARE-19 trial actually showed that dapagliflozin was safe and well tolerated amongst inpatients, allowing for the continuation of the drug when clinically indicated[23]. Regarding outpatient use, the recommendations, as with metformin, are mixed. Some advocate for the discontinuation of SGLT-2i with any level of illness[28,34], while others recommend that they should be continued in mild to moderate illness, because of their significant cardiorenal benefits[29,32]. The position of the Hellenic Diabetes Association is to withhold this drug class during acute illness and that therapy should be re-initiated after clinical improvement[39].

GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS (GLP-1 RA)

Evidence from the UK shows overall no mortality difference with the premorbid use of GLP-1 RA compared to their non-use (HR 0·94 [95% CI 0·83-1·07])[18]. However, when compared to DPP-4i, the N3C study found lower rates of 60-day mortality (OR 0.54 [95% CI 0.37-0.80]), ER visits and hospitalization with GLP-1 RA use[19].

During acute COVID-19, the use of GLP-1 RA remains controversial. Due to the possibility of Gastrointestinal (GI) adverse effects (nausea/vomiting) and the resulting dehydration, some recommend against their use, especially in patients with severe disease that require hospitalization[31-33,35]. On the other hand, GLP-1 RA have been cited as the preferred treatment option for hospitalized patients[34]. This lack of consistency highlights the need for more robust data. If the use of GLP-1 RA is decided, the patient should be monitored for signs of dehydration, and adequate fluid and food intake should be encouraged[28]. As a side note, fixed formulations of either a GLP-1 RA or a SGLT-2i with basal insulin have been proven to be equally effective, and even safer (less hypoglycemic episodes), to a basal-bolus insulin regimen for PWD and inadequate glycemic control[40]. If this could be applied for PWD and COVID-19 remains unanswered.

DIPEPTIDYL-PEPTIDASE 4 INHIBITORS (DPP4-I)

Observational studies show either a negative or a neutral effect regarding the premorbid use of DPP4-i for PWD and COVID-19[18-22,25]. As discussed above, the premorbid use of the DPP4-i class compared poorly to both SGLT-2i and GLP-1 RA regarding the rates of 60-day mortality, ER visits and hospitalization[19]. A meta-analysis of nine studies looked into the effects of the premorbid, but also the in-hospital use of DPP4-i. The results revealed no significant difference in mortality with preadmission use of DPP4-i (adjusted OR 0.89, 95% CI 0.73-1.09), but interestingly found that their in-hospital use was associated with a significant reduction in mortality (adjusted OR 0.27, 95% CI 0.13-0.55)[25]. The reasons for this are not fully understood, but it may be due to the role of DPP4/CD26 acting as a co-receptor for the binding of SARS-CoV-2 to the ACE2-R of human cells, with the use of DPP4-i possibly inhibiting the adherence of the virus[41-43]. Although the decrease in mortality appears important, large randomized, placebo-controlled studies are needed to confirm these findings.

Most recommendations agree that the use of DPP4-i may be continued during acute infection with COVID-19, both in the outpatient and the inpatient setting. The safety profile of these drugs is very favorable and they can be used across a wide range of renal function[28-30,33,34].

SULFONYLUREAS

The premorbid use of sulfonylureas (such as gliclazide) has shown no significant difference in COVID-19 related mortality (adjusted HR 0·94 [95% CI 0·89-0·99]), according to the UK Cohort study[18]. In line with these findings is a study from the US involving 35.000 veterans with T2DM and COVID-19, which also demonstrated a neutral effect of the premorbid use of sulfonylureas on 30-day mortality (OR 1.00, 95% CI 0.92–1.10) [27]. The study also found no difference in the rates of hospitalization and ICU admission(OR 1.02,95% CI 0.96–1.08 and 1.04,95% CI 0.95–1.14, respectively.)[27]

The use of sulfonylureas during acute COVID-19 has not been thoroughly tested, but they should generally be

discontinued when oral intake of food is poor, due to the risk of hypoglycemia[32,33].

THIAZOLIDINEDIONES

As with sulfonylureas, the US Veterans study demonstrated a neutral effect with the premorbid use of thiazolidinediones on hospitalization, ICU admission and 30-day mortality for PWD and COVID-19 (OR 1.04 [95% CI 0.93–1.17], 0.97 [95% CI 0.80–1.19] and 1.07 [95% CI 0.88–1.30], respectively)[27]. Evidence from the UK also showed no difference in COVID-19 related mortality with the premorbid use of this drug class (adjusted HR 0·94 [95% CI 0·82–1·07])[18].

Published recommendations generally suggest that pioglitazone may be continued in mild to moderate COVID-19. However, it should be discontinued in hospitalized individuals with severe or critical disease, due to the risk of fluid retention and possible exacerbation of heart failure[29,30,32,33].

INSULIN

The routine pre-admission use of insulin is associated with an increased COVID-19 mortality[18,22,27]. CORONADO (Coronavirus SARS-CoV-2 and Diabetes Outcomes), a nationwide observational study in France demonstrated an age-adjusted OR of 1.72 (95% CI 1.41, 2.08) with the premorbid use of insulin, regarding the 28-day mortality of PWD hospitalized with COVID-19[22]. The use of insulin was also associated with a reduced chance of hospital discharge within 28 days (age-adjusted OR 0.78 [95% CI 0.67, 0.92])[22]. Similar results have been published by the UK Cohort study, with the premorbid use of insulin being correlated to an increased chance of COVID-19 related death (HR 1·42 [95% CI 1·35–1·49])[18]. A causal relationship between routine insulin use and COVID-19 mortality has not been established, and it is likely that confounders, such as longer diabetes duration, have played an important role in these outcomes[44].

Insulin seems to be the preferred treatment option for hospitalized patients with COVID-19[28-34]. Regular glucose monitoring, or even continuous glucose monitoring is advised to quickly identify hypoglycemia[28,31]. For non-critically ill patients, subcutaneous basal/bolus/sliding scale insulin is the go-to regimen[31,33]. For patients that are critically ill (ICU), insulin is best given as an intravenous infusion[28,30,34]. Evidence shows that the use of insulin (as an infusion) and the resulting control of hyperglycemia leads to lower IL-6 and D-dimer values, as well as improved clinical outcomes for PWD hospitalized with COVID-19[45].

SUMMARY

Table 1 summarizes the recommendations regarding the use of diabetes medications during acute COVID-19. For PWD at risk of infection, but not currently infected, the recommendation is that patients continue on their usual therapeutic regimen. This recommendation is due to the lack of sufficient evidence to guide a change in treatment in this setting[18,30].

TABLE 1. Summary of recommendations for the use of diabetes medications during acute COVID-19.

Drug class	Recommendation
Metformin	Discontinue in severe-critical disease. May be used during mild to moderate disease if there is no severe dehydration
SGLT-2i	May be used in mild to moderate disease, and possibly even in severe disease. Monitor for dehydration and DKA. Avoid in critically ill patients
GLP-1 RA	May be used in mild to moderate disease. More data needed to know if suitable for severe disease
DPP4-i	Can be used across a wide range of disease severity, as generally well tolerated
Sulfonylureas	Discontinue if oral intake of food is poor, due to the risk of hypoglycemia.
Pioglitazone	Continue in mild to moderate disease. Avoid in severe disease due to the risk of fluid retention.
Insulin	Preferred treatment option for hospitalized patients, where it should be given subcutaneously in severe disease, and as an intravenous infusion in critically ill patients. Regular glucose monitoring is advised

Disease severity is described as follows: *Mild* (no pneumonia and SpO2≥94% on room air), *Moderate* (pneumonia with SpO2≥94% on room air), *Severe* (pneumonia and at least one of the following: SpO2≤94% on room air, PaO2/FiO2≤300 mmHg, Respiratory Rate≥30/min, ≥50% lung infiltrates on imaging), *Critical* (ARDS, Sepsis or Septic shock)

SpO2: oxygen saturation, PaO2: partial pressure of oxygen in arterial blood, Fi02: fraction of inspired oxygen, ARDS: acute respiratory distress syndrome

CONCLUSION

Although the COVID-19 pandemic may be receding, with many countries slowly entering the endemic phase of the infection, it remains crucial for PWD to get the best available care, since SARS-CoV-2 infections will continue to appear. Most recommendations regarding the use of diabetes medications are based on observational studies and clinical experience with the use of the various drugs, and thus should be adapted with caution. It would be nice to have more randomized, placebo-controlled studies be conducted, for example regarding the use of GLP-1 RA or DPP4-i in the hospital setting. Common goal is that PWD should have the best available treatment when infected with COVID-19, thus reducing mortality and adding to their quality of life.

Acknowledgment

None

Conflict of Interests

The authors have no conflicts of interest related to this publication.

ΠΕΡΙΛΗΨΗ

Αντιδιαβητική αγωγή σε ασθενή με λοίμωξη COVID-19

Κωνσταντίνος Θεοχάρης[1], Χριστίνα Άντζα[1], Γεώργιος Κωστόπουλος[2], Βασίλειος Κώτσης[1]

[1]Γ' Πανεπιστημιακή Παθολογική Κλινική ΑΠΘ, Νοσοκομείο Παπαγεωργίου, Θεσσαλονίκη, [2]Τμήμα Ενδοκρινολογίας, 424 ΓΣΝΕ, Θεσσαλονίκη

Η πανδημία COVID-19 έχει θέσει νέες προκλήσεις στη διαχείριση της συνεχώς αυξανόμενης ομάδας ασθενών με Σακχαρώδη Διαβήτη (ΣΔ). Ένα σημαντικό ερώτημα που πρέπει να απαντηθεί είναι εάν κάποια συγκεκριμένη υπογλυκαιμική θεραπεία σχετίζεται με χειρότερη ή καλύτερη έκβαση όσον αφορά τη νόσηση COVID-19 σε ασθενείς με ΣΔ. Οι κλινικοί ιατροί έπρεπε να λάβουν τέτοιες αποφάσεις διαχείρισης ελλείψει ισχυρών επιστημονικών στοιχείων μέχρι στιγμής. Μετά από σχεδόν δύο χρόνια πανδημίας, υπάρχει πλέον ένας αξιόλογος αριθμός μελετών, οι οποίες συγκρίνουν την προ της νόσησης ή την ενδονοσοκομειακή χρήση συγκεκριμένων αντιδιαβητικών φαρμάκων, και τη συσχετίζουν με την έκβαση της COVID-19, ενώ επιπλέον υπάρχουν και αρκετές δημοσιευμένες οδηγίες για τη διαχείριση των ασθενών με ΣΔ κατά τη διάρκεια της πανδημίας. Σκοπός αυτής της ανασκόπησης είναι να εξετάσει τη σχέση ανάμεσα στις διάφορες κατηγορίες αντιδιαβητικών φαρμάκων και την έκβαση της COVID-19, καθώς και να δώσει τεκμηριωμένες συστάσεις για τη χρήση των υπογλυκαιμικών θεραπειών κατά τη διάρκεια της οξείας λοίμωξης COVID-19.

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ: *Διαβήτης; Τύπου 2 Σακχαρώδης Διαβήτης; COVID-19; θνητότητα; νοσηρότητα*

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