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THE IMPACT OF THERAPEUTIC DIABETES TREATMENT ON COVID-19 INFECTION: OVERVIEW

Mohamed Abdoul-Latif, Fatouma[1]* ; Ainane, Ayoub[2] ; Houmed Aboubaker, Ibrahim[3] ; Mohamed Ahmed, Nabil[1] ; Ainane, Tarik[2]

[1]Medicinal Research Institute, Center for Research and Study of Djibouti, BP 486, Djibouti.

[2]Superior School of Technology of Khenifra (EST-Khenifra), University of Sultan Moulay Slimane, BP 170, Khenifra 54000 Morocco.

[3]Peltier hospital of Djibouti, BP 2123, Republic of Djibouti.

*fatouma_abdoulatif@yahoo.fr

Abstract

Based on currently available epidemiological data, diabetes does not appear to be a risk factor for SARS-CoV-2 infection. However, it is associated with a more severe disease mainly due to its high prevalence in the elderly and polymorbid people, whose course is more often unfavorable. As with any other infection, pre-existing diabetes, especially if poorly controlled, can promote secondary infections and lead to acute complications related to hyperglycemia, which is itself aggravated by the infection. It is important to recommend that patients have enough supplies at home, take regular self-measurements of blood sugar, and contact a caregiver immediately if there is a blood sugar imbalance or infection. Antidiabetic treatment should be adapted as usual in case of infection. Insulin therapy should be considered for persistent hyperglycemia in any patient hospitalized with acute infection.

Keywords: *Diabetes; treatment, infections; factor; COVID-19; SARS-CoV-2.*

Introduction

The new SARS-CoV-2 coronavirus (COVID-19) causing severe acute respiratory syndrome, responsible for the current global pandemic, is the subject of many questions, both for patients and for caregivers **[1-3]**. Due to the rapid spread of the virus, little epidemiological data is currently available **[4]**. Some scientific articles, mostly Asian and African, have suggested that diabetes is one of the most common comorbidities among patients with the disease **[5-7]**. Diabetes had previously been described as a major risk factor for an unfavorable outcome during the two previous coronavirus infections: SARS in 2002, which affected more than 8,000 people mainly in Asia, as well as Middle respiratory syndrome. Orient (MERS) in 2012, which affected more than 2,000 people, mainly in Saudi Arabia **[8-10]**. The objective of this article is to clarify the impact of diabetes on COVID-19 disease, to provide guidance on anti-diabetic treatments, as well as to suggest some measures to recommend to diabetic patients **[11-12]**.

Epidemiology

Available epidemiological data shows that elderly patients and those known to have chronic diseases, such as diabetes, hypertension, coronary heart disease, cerebrovascular disease, appear to be at greater risk for severe COVID-19. We note, in the initial Chinese data and according to the authors, 12 to 22% of diabetes among affected patients **[13-15]**. These data are confirmed with those from the Centers for Disease Control and Prevention in the United States showing a prevalence of diabetes of 6, 24 and 32% in COVID-19 positive people, respectively not hospitalized, hospitalized without intensive care, and hospitalized with care. Intensive **[16]**. One of the pathophysiological hypotheses is the increased expression of angiotensin-converting enzyme 2 (ACE 2) in patients with diabetes, both type 1 and type 2. This enzyme, expressed in the lungs. The intestine, the kidneys and the blood vessels, would be preferentially linked by SARS-CoV-2 and could explain a more serious damage in certain groups of patients **[17-19]**. In addition, hyperglycemia, whether acute or chronic, is known to alter the response of the immune system, leading to an exaggerated pro-inflammatory response, a condition that has been demonstrated in patients with severe COVID-19. In addition, this relationship between diabetes and severe forms of COVID-19 is also due to a statistical association: the most severe forms or deaths are mostly seen in patients over 65, a population in which the prevalence of diabetes is high. As such, around a quarter of people over the age of 75 have type 2 diabetes **[20-21]**.

Risks in case of COVID-19 infection

Is the diabetic patient at greater risk of contracting a COVID-19 infection?

There is currently no evidence that the risk of COVID-19 is higher in people with diabetes. Indeed, the prevalence of diabetes in non-hospitalized COVID-19 positive people is comparable to that of the general population **[22-23]**.

Why are diabetic patients categorized in at-risk populations?

On proven risk of severe disease

The risk of developing a severe form is higher in people with diabetes, especially if they have other co-morbidities. Indeed, diabetic patients appear to be at greater risk of an unfavorable outcome **[23].** In the first Chinese studies reporting the rate of diabetic patients in the infected population, diabetes appears to be 2.26 times (95% CI: 1.47-3.49) more common in patients with more severe infection compared to those with less severe infection. Chinese data show that diabetes confers an odds ratio of 2.85 (95% CI: 1.35-6.05) of in-hospital mortality **[24]**. These data, on case-control studies, overestimate, with the calculation of the odds ratio, the relative risk of death if the presence of diabetes **[25-27]**. They are not always adjusted for age, which is a major confounding factor in the prevalence of diabetes **[28]**. In Italy, a prevalence of diabetes of 35.5% is noted in patients who died from COVID-19, in a median age population of 80.5 years (interquartile range; IQR: 31-103) and predominantly male (70 %). Comparing with the incidence of diabetes in the same segment of the population in Italy in 2018 (20.3%), the authors report a relative risk of diabetes of 1.75 in patients who died from COVID-19.10 Finally, it is to note that, in a recent analysis, the blood sugar level was not associated with the severity of COVID-19.11 It is therefore

necessary to emphasize the advanced age of patients with severe disease, as well as their multiple comorbidities, defining them as a population particularly at risk **[29-30]**.

Increased risk of superinfection or complications from diabetes

In diabetic patients, this increased risk of developing complications from viral infection is well known and the vaccination against seasonal influenza or *Pneumococcus* is recommended. Being vaccinated against the flu reduces the risk of going to a hospital for a stroke by 30%, for a myocardial infarction by 22% and for pneumonia by 15%. Mortality is also reduced by 24% **[31]**.

Increased risk of diabetic decompensation

In the event of an acute infection, a state of insulin resistance sets in and requires an adaptation of the antidiabetic treatment, sometimes with insulin relay in patients usually treated with oral antidiabetics (ADO), or an increase in pre-existing insulin therapy. In all diabetic patients, infection with SARS-CoV-2 will therefore be associated with an increased risk of ketoacidosis or hypersomolar decompensation **[32]**.

Is there a risk associated with antidiabetic treatment?

To date, neither ODA nor insulin has been associated with an increased risk of SARSCoV-2 infection, or an adverse course **[33]**. In diabetic patients treated only with ADO, if treatment were to be continued in a septic context and in particular in the absence of food intake, there are risks depending on the type of treatment (Table 1). Finally, in cases of severe SARS-CoV-2 infection requiring hospitalization and antiviral treatment, some ODAs require monitoring in the event of concomitant use of atazanavir or lopinavir / ritonavir **[34]**. The concomitant use of repaglinide and atazanavir is even contraindicated (Table 2).

Specific measures for patients

The patient will follow the barrier measures issued by the OFSP: social distancing, frequent hand washing, limited outings. The caregiver can issue a certificate asking the employer to comply with OFSP guidelines for people with diabetes in contact with the public, by promoting teleworking or by providing masks and gloves for more optimal protection **[35]**.

Adaptation of treatment

First, in the absence of severe infection, it is important to recommend that patients continue to take their usual diabetes medication. This is valid for other drugs, in particular cholesterol lowering drugs and antihypertensives **[36]**. For blockers of the renin-angiotensin system (ACE inhibitors and sartans), continued treatment is recommended. While the ACE 2 enzyme appears to be one of the coronavirus receptors in the respiratory tract, there is currently no scientific evidence that blockers of the renin-angiotensin system influence the course of the disease (Table 3) **[37]**. As mentioned previously, in the event of illness inducing a reduction in food intake or hydration, it will be necessary to reduce or even stop certain anti-diabetic treatments (Table 1). In the event of persistent hyperglycaemia, it will be indicated to adapt the ADO treatment or the insulin. We recommend that all diabetic patients contact their doctor or attending diabetologist to discuss any treatment adjustment if necessary. These adaptations can be easily made by telemedicine.

Material

In order to avoid regular outings during partial confinement, we recommend that patients have sufficient supplies at home for at least two weeks (e.g. in case of infection with COVID-19), both in material than oral or injectable drugs. Thus, in the event of confinement due to a mild form of the disease, no exit will be necessary **[38]**. We will remind them to have alcohol swabs, additional hand sanitizers, as well as capillary blood glucose test strips and lancets, monitoring equipment, needles, catheters and reservoirs, batteries. For insulinopenic patients at risk of developing ketosis, particularly in the event of infection, we also recommend having urine and / or capillary strips (preferably) to control ketone bodies and to review with their doctor the adjustment of the doses in hyperglycemia with or without ketonemia. Due to the anorexia that may be present during the disease, the risk of hypoglycemia may be increased. It will therefore also be advisable to have glucagon in reserve. Finally, it is helpful to remind any patient to keep a supply of fast-

swallowing carbohydrates separate from other foods in the house and easily accessible.

Glycemic monitoring and contact with professionals

During this epidemic, the hygiene-dietetic habits being particularly modified, an increased monitoring of the glycemia is recommended. The names and telephone numbers of treating physicians, as well as any other caregivers in the multidisciplinary diabetology team, must be easily accessible, so that they can be reached if necessary (Table 4). In the event of an urgent consultation, the caregiver will respect the hygiene guidelines issued by the authorities. Therapeutic follow-up is essential to avoid hospitalizations. Foot care in particular should be continued if there is a risk of hospitalization for plantar perforator disease. The disruption of the continuity of care in unbalanced or complicated patients puts them at a higher risk of severe diabetic decompensation than that linked to COVID-19 **[39-40]**.

What to do in case of symptoms suggestive of COVID-19?

It is important to educate patients on the symptoms to be recognized, which are heterogeneous and may include fever, cough, but sometimes just flu-like or gastrointestinal symptoms. Often, the patient will notice an increase in blood sugar and / or insulin requirements sometimes preceding the signs of infection themselves. If an infection is confirmed without signs of seriousness, careful monitoring of glucose and ketones in the event of prolonged hyperglycemia, as well as the resulting corrective measures, is imperative. Close telephone contact with a caregiver will be considered (Table 4) **[40]**.

During regular treatment with paracetamol, we recommend that patients with certain Continuous Glucose Monitoring (CGM) systems, such as Dexcom G5, Medtronic Enlite and Guardian, be reminded that this treatment may alter the displayed blood glucose values. In case of doubt, monitoring by capillary glycemia or more frequent calibrations are to be proposed.

Hospitalization and glycemic control

In view of the risk of glycemic imbalance induced by insulin resistance in connection with the infectious context, we recommend strict monitoring of blood glucose levels in all patients known to have diabetes, even on ADO monotherapy. HbA1c and ketonemia should be measured in patients with elevated blood sugar levels, whether or not known to have diabetes. In patients on SGLT-2 inhibitors, ketonemia is essential on admission, even if the blood sugar is normal, as euglycemic ketoacidosis can occur with decompensation. In the event of persistent hyperglycaemia, discontinuation of ADO treatment should be considered, with a transient relay by basal-bolus insulin therapy (Table 4). Strict glycemic control being associated with a decrease in morbidity and mortality in intensive care patients, intravenous insulin therapy with strict targets (7-10 mmol / l) will be necessary in some patients, sometimes even at high doses, due to increased insulin resistance. Close contact with the multidisciplinary intra-hospital diabetology team at your center should be planned **[41-43]**.

Conclusion

Diabetes is associated with a more severe and unfavorable course of SARS-CoV-2 infection. It is important to note that this population with severe complications is often elderly and suffers from other major comorbidities, often metabolic and cardiovascular. There is no indication to change the anti-diabetic treatment to prevention. However, strict monitoring and glycemic control recommendations should be made in the event of infection. In severe cases, non-insulin antidiabetics all present their own risks. The use of intensified insulin therapy will therefore be necessary to aim for glycemic control, protecting the patient from the risk of secondary infection. We recommend reviewing with patients the need for sufficient supplies at home, regular self-monitoring of blood sugar, and contacting a caregiver immediately in the event of blood sugar imbalance or infection.

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Table 1. Oral antidiabetics: risks and recommendations in the event of COVID-19.

Class	Risks	Recommendations
Metformin	Lactic acidosis	Discontinue if inappetence, diarrhea, vomiting, or kidney failure acute (eGFR <60 ml / min).
Sulfonylureas, glinides	Hypoglycemia	Discontinue if inappetence or acute renal failure (eGFR <60 ml / min).
DPP-4 inhibitor	Not known	Discontinuation in severe acute renal failure (eGFR <30ml/min, unless linagliptin = can be continued even in end-stage renal failure).
GLP-1 receptor agonist	Nausea, vomiting, anorexia	Discontinue if inappetence, nausea, vomiting, or acute renal failure (eGFR <15ml / min).
SGLT2 inhibitor	Dehydration, acute renal failure, hyperglycemic or euglycemic ketoacidosis	Discontinue if fever, inappetence, nausea, vomiting, or acute renal failure (eGFR <45 ml / min).

DDP-4: dipeptidyl peptidase-4; eGFR: estimated glomerular filtration rate; GPL-1: glucagon-like peptide-1; SGLT2: sodium-glucose co-transporter 2.
NB: due to their very rare use, acarbose and thiazolinediones have not been included in this table.

Table 2. Interactions between oral antidiabetics and antivirals in COVID-19.

Class	Known interactions
Metformin	None.
Sulfonylurea	• Glibenclamide: risk of increased effect in the event of co-medication with atazanavir or lopinavir / ritonavir. • Gliclazide: risk of reduced effect in the event of co-medication with lopinavir / ritonavir. • Glimepiride: risk of reduction in effect in case of comedi cation with lopinavir / ritonavir.
Glinide	• Nateglinide: risk of increased / reduced effect in the event of comedication with atazanavir or lopinavir / ritonavir. • Repaglinide: contraindicated if comedication with atazanavir, risk of increased effect in the event of comedication with lopinavir / ritonavir or favipiravir.
DPP-4 inhibitor	• Saxagliptin: risk of increased effect when taking medication with atazanavir or lopinavir / ritonavir.
GLP-1 receptor agonist	• Dulaglutide: risk of reduced effect of atazanavir. • Exenatide: risk of reduced effect of atazanavir. • Liraglutide: risk of reduced effect of atazanavir.
SGLT2 inhibitor	• Canagliflozin: risk of reduction of the effect in case of medication with lopinavir / ritonavir.
Insulin	None.

DDP-4: dipeptidyl peptidase-4; GPL-1: glucagon-like peptide-1; SGLT2: sodiumglucose co-transporter 2.
NB: due to their very rare use, acarbose and thiazolineediones have not been included in this table.

Table 3. COVID-19: Controversies about some drugs.

Blockers of the renin angiotensin system
• The angiotensin-2 converting enzyme (ACE-2) is used by the SARS-CoV-2 virus as a receptor to enter cells: its overexpression could increase the risk of viral infection. • The expression of ACE-2 is however protective against the risk of inflammation causing the most severe forms of COVID-19 infection.
DPP-IV inhibitors
• DDP-IV has been identified as a possible receptor for the coronavirus Erasmus Medical center responsible for MERS. Inhibition of DPP-IV may reduce the risk of infection with this virus. • Inhibition of DPP-IV may reduce inflammation especially in type 2 diabetics. • However, DPP-IV inhibitors are associated with an increased risk of upper respiratory infections without increasing the risk of lung disease.
Statins
• Statins increase the level of ACE-2 expression. • Statins have shown an anti-inflammatory effect via inhibition of NF-Kappa B and may have a preventive role in the pro-inflammatory cytokine storm that causes severe forms of COVID-19.

NB: As the data concerning the drugs listed below are purely experimental and in the absence of a current clinical argument, no adaptation of these treatments is recommended in the context of the current pandemic.

Table 4. Management of diabetic patients, infected or not.

Uninfected patients
• Therapeutic optimization: glycemic objectives between 4 and 10 mmol / l,> 70% in the target (50% in the most fragile), <4% hypoglycemia. • No discontinuation of treatment in progress. • Increased self-monitoring. • Material and insulin reserves. • Reinforced protection measures. • Consultation for follow-up and advice. • Protocols and emergency numbers available.
Patients with moderate form
• Close glycemic monitoring: frequent teleconsultations. • Glycemic targets between 4 and 10 mmol / l,> 70% in target), <4% hypoglycemia. • Insulin therapy possible with discontinuation of oral antidiabetic drugs at risk if comorbidities or increased fragility. • Protocols and emergency numbers available.
Patients with severe form
• On admission: blood sugar, potassium, ketonemia (beta-hydroxybutyrate or capillary ketones), HbA1c, pH. • Initiation of insulin treatment in any patient with glycemia> 10 mmol / l. • Stop taking oral antidiabetics. • Relay by intensive insulin therapy. • Glycemic targets between 7.8 and 10 mmol / l.