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# Post COVID-19 syndrome related to diabetes – A brief review

A.P. Stoian[1]*, M. Rizzo[2]*, T. Salmen[3]*, P. Kempler[4], T. Stulnig[5], N. Papanas[6], D. Popovic[7], C. Herder[8, 9, 10], D. Serban[11]

## Abstract

The COVID-19 pandemic, as named by the World Health Organization, emerged in 2019 in Wuhan, China, secondary to the spread of the novel coronavirus, SARS-CoV-2, that has a human-to-human manner of transmission, with a high transmissibility rate and a lower fatality rate compared to other respiratory syndromes. Patients with diabetes are more susceptible to the most severe complications of COVID-19 and related mortality. The management and treatment of diabetes have been quite difficult during this long COVID-19 pandemic for many reasons, including the reduced patients` access to health care facilities for their regular scheduled visits, leading to excess mortality that has been early reported. Novel antidiabetic drugs such as GLP-1RAs and SGLT-2i may have some beneficial actions on COVID-19 outcome, potentially even interfering with the viral action; yet, many uncertainties still exist about the so-called post-COVID-19 syndrome, for which the diagnostic and therapeutical approach is still not fully defined. Therefore, we need to use the experience gained from the recent events to guide our current and future clinical work and give our patients with diabetes and cardiometabolic diseases better quality of life during COVID-19 and post-COVID-19 time.

**Keywords:** COVID-19, diabetes, treatment, prevention, complications, post-COVID-19.



1) Department of Diabetes, Nutrition and Metabolic Diseases, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
2) Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties Promise), University of Palermo, Italy
3) Department of Diabetes, Nutrition and Metabolic Diseases, "Prof.N.C. Paulescu" National Institute of Diabetes, Nutrition and Metabolic Diseases, Bucharest, Romania
4) Department of Medicine and Oncology, Faculty of Medicine, Semmelweis University, Budapest, Hungary
5) Department of Medicine III and Karl Landsteiner Institute for Metabolic Diseases and Nephrology, Clinic Hietzing, Vienna Healthcare Group, Vienna, Austria
6) Diabetes Centre, Second Department of Internal Medicine, Democritus University of Thrace, University Hospital of Alexandroupolis, Greece
7) Clinic for Endocrinology, Diabetes and Metabolic Disorders, Clinical Center of Vojvodina & Medical Faculty, University of Novi Sad, Serbia
8) Institute for Clinical Diabetology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University Düsseldorf, Düsseldorf, Germany
9) German Center for Diabetes Research DZD), Partner Düsseldorf, München-Neuherberg, Germany
10) Department of Endocrinology and Diabetology, Medical Faculty and University Hospital Düsseldorf, Heinrich Heine University Düsseldorf, Düsseldorf, Germany
11) Department of General Surgery, Carol Davila University of Medicine & Forth Department of General Surgery, Emergency University Hospital, Bucharest, Romania.

* The authors contributed equally and share the first authorship

## Overview of COVID-19 pandemic

The coronavirus disease 2019 (COVID-19) pandemic, as named by the World Health Organization, emerged in 2019 in Wuhan, China, secondary to the spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), that has a human-to-human manner of transmission, with a high transmissibility rate and a lower fatality rate as compared to other respiratory syndromes [Deng 2020]. The dominant symptoms are fever, dyspnea, followed by cough and chest tightness/pain [Deng 2020, Huang 2021, Gupta 2020, Richardson 2020]. The most frequent comorbidities of hospitalized patients include high blood pressure, diabetes mellitus (DM), cardiovascular disease (CVD) and chronic lung disease [Deng 2020, Gupta 2020, Richardson 2020, Bajgain 2021]. Due to the limited effectiveness of non-pharmacological measures, and the limited availability and efficacy of antiviral drugs against COVID-19, vaccination is the primary way to obtain control over the pandemic and limit the severity of COVID-19 cases [Christie 2021].

## Risk factors for COVID-19 infection

Patients with DM do not seem to have a higher risk of COVID-19 infection than the general population, possibly because they are more prone to adhere to gener-

al non-pharmacological measures [Unnikrishnan 2021, Sourij 2021]. On the other hand, the presence of older age, male sex, hypertension, CVD, or any stage of hyperglycemia represent predisposing factors for worsening outcomes, from a more severe form of COVID-19, higher mortality reflected by need to intensive care unit admission or need for mechanical ventilation, to just a more severe respiratory involvement [Gupta 2020, Unnikrishnan 2021, Sourij 2021, Fadini 2020, Costa 2020, Apicella 2020, Schlesinger 2021].

Patients with DM and those with CVD as well as with different components of the metabolic syndrome are seriously affected by the pandemic because of the public health measures taken to limit its development, such as lockdowns. In these situations, even if there may be a slight increase in the number of physical activities undertaken, a net increase to a sedentary lifestyle with more difficult access to clinical care or options to provide a healthy diet was observed [Unnikrishnan 2021, van Bakel 2021, Cannatà 2021].

From the treatment point of view, it is essential to achieve good blood-glucose management by a regular follow-up in ambulatory settings. The most therapeutic schemes with antidiabetic drugs can be maintained, under the recommendation of adequate hydration and nourishment, if there is a mild-moderate form of COVID-19. Still, in case of severe forms that may request hospitalization, switching over to insulin therapy may be necessary [Unnikrishnan 2021, Apicella 2020, Abdi 2020].

## New-onset DM and aggravated DM post COVID-19

DM is one of the most common comorbidities associated with the severity of COVID-19 infection and also a risk factor for a poorer prognosis, due to the development of the most severe forms of the disease and with an increase in its related mortality [Apicella 2020, Muthukrishnan 2021].

COVID-19 infection is a risk factor for developing new-onset hyperglycemia, worsening glycemic control and the possibility of the appearance of severe metabolic complications, such as hyperosmolar status or diabetic ketoacidosis, in pre-existing DM or even manifestation of de novo DM [Fadini 2020, Costa 2020, Apicella 2020, Muthukrishnan 2021]. Several mechanisms were described, such as direct pancreatic inflammatory damage of the β-cells, the body's stress response to infection by hyperglycemia or by insulin resistance (IR) activity, the need for the use of treatment such as corticosteroids (diabetogenic drugs) for severe forms of COVID-19 [Fadini 2020, Costa 2020, Muthukrishnan 2021, Yang 2006, Steenblock 2021].

As far as the treatment of type 2 DM (T2DM) is concerned, novel antidiabetic drugs like glucagon-like peptide-1 re-

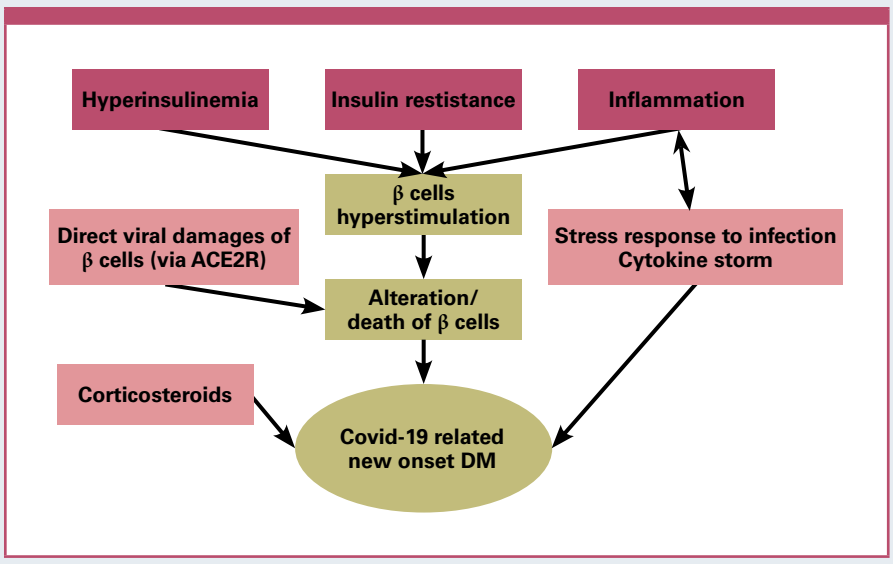


**Fig. 1: The potential mechanisms involved in Covid-19 related new onset diabetes.**

ceptor agonists (GLP-1RAs) and sodium-glucose co-transporter-2 inhibitors (SGLT-2i) have recently shown some beneficial actions on COVID-19 outcome [Popovic 2021], and may potentially even interfere with the viral action [Banerjee 2021]; however, the presence of severe hyperglycemia undoubtedly requires use of insulin therapy.

## The post-COVID-19 syndrome (PCS)

During and/or after more than 12 weeks of a COVID-19 infection, there may be presence of debilitating symptoms and signs that are covered by the so-called post-COVID-19 syndrome (PCS). The most frequent symptoms are headache, weakness, fatigue, myalgia and breathlessness. The onset of these symptoms may happen anytime, and there are different types of long COVID-19 syndrome. The most debated aspects that need further investigation in order to establish if the main mechanisms are related to DM or COVID-19 are postural tachycardia syndrome (PTS) and muscle weakness, which is contributing to fatigue; microvascular complications of DM, affecting eyes, nerves and kidneys, are aggravated by the microvascular involvement of COVID-19 and seem to be interrelated with PTS and fatigability [Raveendran 2021]. Since patients with DM and COVID-19 are fragile, rehabilitation is a long-term multidisciplinary challenge and should include prevention of exacerbation of other comorbidities, a tight glycemic control, proper nutritional intake, especially in protein, vitamins and micronutrients and physical activity in an individualised manner which should include aerobic and resistance exercises along with chest physiotherapy [Raveendran 2021].

## Cytokine storm and inflammation

People living with type 2 DM (T2DM) have an altered immune function, with the defects present in both innate and adaptive cellular immunity [Erener 2020]. Cytokine storm is a life-threatening systemic inflammatory syndrome involving elevated circulating cytokine levels and immune-cell hyperactivation that can be triggered by various pathogens, cancers, autoimmune conditions, monogenic disorders, and therapies [Erener 2020]. It results from an imbalance in cytokine production intended to eliminate the pathogen, which leads to a hyperinflammatory response causing clinically significant collateral damage [Fajgenbaum 2020].

The rapid clinical deterioration and high risk of mortality in severe cases of COVID-19 could be attributed to the development of a cytokine storm [Kim 2021]. Shortly, the most plausible mechanism by which SARS-CoV-2 infection leads to the onset of cytokine storm is an ineffective response of type-I/III interferons to the initial viral infection, which leads to an excessive late immune response [Kim 2021]. Conditions characterized by low-grade chronic inflammation such as T2DM, hypertension, and obesity, are associated with an increased risk of cytokine storm development [Carlos 2021].

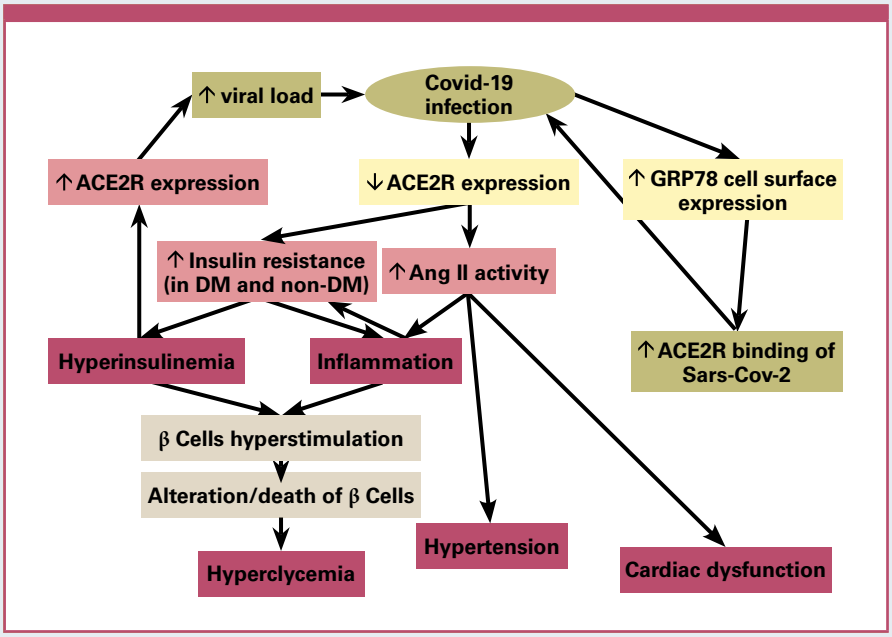


**Fig. 2: The possible link between Covid-19 infection and hyperglycemia, hypertension and cardiac dysfunction.**

## Adipose tissue and GRP78

Glucose-regulated protein 78 (GRP78), also known as immunoglobulin heavy chain binding protein, owns a signal peptide sequence acting as a molecular chaperone on the endoplasmic reticulum [Lee 2005]. It has a critical role in protein folding functions. Still, GRP78 becomes overexpressed and translocated to the cell surface under stressed conditions, where it acts as a receptor for various endogenous and exogenous ligands [Lee 2005].

The available clinical data suggest that GRP78 levels significantly increase in COVID-19 patients [Köseler 2020, Palmeira 2020, Sabirli 2021]. Furthermore, the molecular docking analyses pointed out the putative interaction between GRP78 and the receptor-binding domain of the SARS-CoV-2 spike protein [Ibrahim 2020]. Further experimental data indicate that not only GRP78 is a promoter of SARS-CoV-2-spike-angiotensin-converting enzyme 2 (ACE2) binding, but it also facilitates cell surface ACE2 expression [Carlos 2021].

Interestingly, the recent experimental study, which confirms that SARS-CoV-2 spike protein physically interacts with cell surface GRP78, also shows that GRP78 is highly expressed in adipose tissue due to hyperinsulinemia in adipocytes and is increased both in humans and mice that are older, obese, and have DM [Shin 2021]. This could also give an insight into understanding the association between advanced age, obesity, and T2DM with greater COVID-19 severity and mortality.

## Insulin resistance and β-cell dysfunction

Sensitivity of target tissues to insulin action is notably impaired during SARS-CoV-2 infection among persons already suffering from T2DM and in individuals with no previous history of DM [Montefusco 2021]. On the other hand, hyperinsulinemia can lead to an increased SARS-CoV-2 viral load due to the impact of insulin on the increment of ACE2 membrane expression [Govender 2021]. However, once SARS-CoV-2 infection has been established, ACE2 expression becomes decreased with subsequent exaggeration in the activity of angiotensin II, resulting in deterioration of insulin sensitivity [Finucane 2020]. This leads to IR, oxidative stress, inflammation, hypertension, and cardiac dysfunction [Ceriello 2020]. The association between IR and increased inflammation is bidirectional, as IR increases inflammation and vice versa. Additionally, an overactive immune response leading to a proinflammatory milieu and consequent IR provokes β-cell hyperstimulation, alteration of β-cell function, and potentially its death (Figure 1).

As mentioned beforehand, besides deterioration of preexisting hyperglycemia, COVID-19 can be a trigger for new-onset DM. This glucometabolic distress appears to be mediated by the prolonged persisting abnormality of secretome, resulting in increased IR and β-cell exhaustion caused by hyperstimulation and glucose toxicity [Montefusco 2021]. (Figure 2). It remains to be seen whether new-onset DM may be a long-term complication of COVID-19 which could be associated with a significant health, social, and economic burden in the future.

## Conclusion

In conclusion, patients with DM are more susceptible to the most severe complications of COVID-19 and related mortality [Ceriello 2020, Stoian 2020(a), Aziz 2021]. The management and treatment of DM have been quite difficult during this long COVID-19 pandemic time for many reasons, including the reduced patients' access to health care facilities for their regular scheduled visits [Al Mahmeed 2021], leading to large excess mortality that has been early reported [Rizzo 2020]. Novel antidiabetic drugs like GLP-1RAs [Stoian 2020(b)] and SGLT-2i may have some beneficial actions on COVID-19 outcome [Popovic 2021], and potentially even interfere with the viral action [Banerjee 2021]. Yet, many uncertainties still exist about PCS, for which the diagnostic and therapeutical approach is still not fully defined. We need to use the experience gained from the recent events in order to guide our current and future clinical work [Stoian 2021], and to give a better quality of life to our patients with DM and cardiometabolic diseases during the challenging COVID-19 and post-COVID-19 time.

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**Korrespondenzadresse**
Djordje S. Popovic, MD, PhD
Clinic for Endocrinology, Diabetes and Metabolic Disorders
Clinical Center of Vojvodina
Hajduk Veljkova 1
21000 Novi Sad, Serbia
Tel: +38163551606; Fax: +38121525081
E-mail: pitstop021@gmail.com; djordje.popovic@mf.uns.ac.rs