

# Diabetes mellitus type 2 and COVID-19 pandemic

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Ioulia Sirokosta

*“Man may be the captain of his fate,  
but he is also the victim of his blood sugar”*

Wilfred G. Oakley

From antiquity to the present day, infections have been among the most devastating challenges that humans have to cope with. Millions of people have died from epidemics caused by deadly viruses. Today the human race is being severely tested by the COVID-19 pandemic. Since the beginning of the 21<sup>st</sup> century, this is the third time that a beta coronavirus threatens the human population with a fatal pandemic [1]. Early during the epidemic, it was found that older and frail individuals with chronic diseases are more likely to exhibit more severe symptoms and worse outcome [2]. A medical history of Diabetes Mellitus (DM) was confirmed as a condition with a worse outcome when these individuals are affected by COVID-19 infection [2]. Nowadays, DM prevalence is fairly high in many parts of the world and in view of the COVID-19 pandemic, it is essential to assess the risks implicated on comorbid medical conditions. Almost 500 million people have DM globally and in the future this number is expected to rise dramatically [3]. Although individuals with diabetes have the same possibility as everyone else to get infected by the virus [4], it seems that they manifest a more severe disease; a number of them get hospitalized and often are treated in intensive care units with a high mortality rate [2]. In one of the largest retrospective, multicenter cohort studies from China, 44,672 individuals were found to

be affected by the COVID-19 infection and the overall case fatality ratio (CFR) was 2.3%, while for diabetics this rate was 7.3% [5]. Recently, the high fatality in diabetics was also corroborated by the CORONADO study [6]. A multicenter study from 53 hospitals in France, included 1,317 adult diabetic (89% had type 2 and 3% had type 1) inpatients, admitted between 10 - 31 March 2020, with a laboratory confirmation of COVID-19 [6]. The study showed that one in ten patients died in the first week of hospitalization, while 20% of patients were severely affected and required mechanical ventilation as compared to 5% of non-diabetics [6].

The main question that needs to be answered is whether DM per se, increases infection susceptibility, worse outcome or fatality that can be correlated with bad glucose control. Micro and macro vascular complications, age or obesity often coexist with diabetes, mainly DM type II [7]. Moreover, DM can affect the immune system's ability to fight infection due to alterations in cytokine profile and changes in immune-responses including T-cell and macrophage activation [8]. Lower respiratory tract infections including tuberculosis, are more prevalent in individuals with DM [9]; one third of diabetics treated for infection are diagnosed with pneumonia and, have a high risk for being diagnosed with pneumococcal pneumonia with an increased hospitalization rate. DM individuals also have an increased risk for influenza, often with a severe clinical course and

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Division of Infectious Diseases, Department of Internal Medicine, University Hospital of Patras, Patras, Greece

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more frequent complications [10]. Diabetes is associated with structural changes in patients' lungs including increased vascular permeability and alveolar damage [11].

In the current pandemic of SARS-CoV-2, these observations are re-confirmed [2,4,5]. Bad glycaemic control does not seem to be a key factor for worse outcome in a French study [6]. However, this evidence remains controversial as it is well documented in other studies that hyperglycemia affects innate immunity and impairs macrophages and neutrophils function [7,8,12]. In support of this, studies pertaining to influenza virus infections suggest that high blood glucose levels enhance viral replication [10]. It has been postulated that glycosylated end products, like glycosylated transmembrane protease/serine subfamily member 2 (TMPRSS2), may facilitate SARS-CoV-2 entry into the host cell [13]. Hyperglycemia and insulin resistance are characterized as chronic low-level inflammatory conditions that may lead to enhanced levels of inflammation following SARS-CoV-2 infection [7,11]. Hyperglycemia is generally associated with a significant reduction in forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) [11]. Hyperglycemia is directly implicated in cardiovascular and renal diabetes complications [12]. In the CORONADO study, the complication rate affecting the eyes, kidneys and nerves was 47%; on the other hand, macrovascular complications affecting arteries, heart problems, stroke or leg ulcers, was 41% [6]. When one group of complications as outlined above are observed, the mortality rate increases by two-fold during the first week of hospitalization [6]. DM complications, such as kidney failure and cardiovascular disease, have been shown to increase the severity of COVID-19 disease and the risk of death [2,6,12]. Obesity is often present in most cases of DM, especially in adults with insulin resistance [14]. The connection between abdominal obesity, insulin resistance and inflammation are well documented; abnormal secretion of adipokines, pro-inflammatory cytokines (TNF- $\alpha$ , IL-1 $\beta$ , IL-6, IL-8, IL-12 and interferons) and acute phase reactants are increased in the serum, causing a reduced immune response [8,14,15].

According to these findings, obese individuals with DM are more susceptible to an inflammatory cytokine storm eventually leading to acute respiratory distress syndrome (ARDS), shock and rapid deterioration of their health status. In parallel, obese individuals experience a restrictive respiratory function, due to thickness and may more readily require mechanical ventilation [14,15].

Age is an independent risk factor of worse outcome

in all individuals affected by COVID-19 [2,4,5,6]. Persons older than seventy-five years old with DM have a 14-times higher risk to die when infected with COVID-19 than those with an age of less than 55 years old [6].

Management of DM patients infected with SARS-CoV-2 is quite challenging. Viral infection may cause a sharp fluctuation of blood glucose levels in DM patients, increasing stress hormones which may adversely affect recovery [7,9]. Based on a study carried out in Wuhan, hypoglycemia (<3.9 mmol/L) accounts to approximately 10% of hospitalized patients, leading to platelet activation and thrombosis [12]. On the other hand, SARS-CoV-2 virus can also directly cause  $\beta$ -cell damage due to abundant ACE2 cellular expression which facilitates the entry of the virus into these cells eventually leading to cell death [7]. Higher D-dimer levels have been reported in COVID-19 patients with DM, leading to rapid progression, adverse prognosis and outcomes [7]. COVID-19 infection is associated with hypokalemia, hyperglycemia and hypertension because of high aldosterone levels [16]. The International Diabetes Federation puts great emphasis in optimal glucose levels monitoring especially during the pandemic period. Specialists suggest insulin treatment during the prolonged hospitalization periods in these patients [17]. Continuous monitoring of blood glucose levels and ketone levels are required to prevent hyperglycemia, hypoglycemia ketoacidosis and non-ketotic hyperosmotic coma. Although, previous studies have reported better outcome in DM patients receiving metformin when affected by lower respiratory tract infections [14], these individuals should discontinue treatment in case of fever, because of lactate acidosis risk [17]. The sodium glucose co transporter 2 (SGLT-2) has been implicated in the pathogenesis of euglycaemic ketoacidosis and there is a risk of dehydration (fever, vomiting) [17]. Pioglitazone and long-acting glucagon-like peptide-1 (GLP-1) receptor agonists (like liraglutide) are not recommended during acute infection, as they have been associated with angiotensin-converting enzyme 2 (ACE2) up regulation in animal studies [12,13,17]. The beneficial or adverse effect of ACE inhibitors/ARBs treatment remains unclear. The American Heart Association suggests continuous treatment in case of patients with COVID-19 infection [7]. Although no treatment has been approved for SARS-CoV-2, hydroxychloroquine may be beneficial to diabetics, as studies have reported that hydroxychloroquine block virus-cell fusion and improves glycaemic control.

## CONCLUSIONS

COVID-19 infection leads to worse outcome in DM patients. Therefore, it is imperative that people with diabetes take all the necessary precautions (e.g. vaccines) and achieve good glycaemic control, as judged by measuring HbA1c, in the midst of the ongoing pandemic. Special attention should be paid to individuals with DM older than 70 years, obese with heart and kidney complications. Personal hygiene, social distancing, diabetic diet with low calories, daily exercise, adequacy of medicine and supplements are strongly suggested. Also, ensuring confidentiality and sufficient access to personal doctor during a pandemic are required. Lastly, it is fundamental to mention that good glycaemic control is also crucial for patient's good prognosis during their hospitalization.

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### Corresponding author:

Ioulia Sirokosta  
 Division of Infectious Diseases,  
 Department of Internal Medicine, University Hospital of Patras,  
 Patras, Greece  
 Tel.: +30 261999744, Fax: +30 2610999740  
 E-mail: juliasirokosta@yahoo.com