

## COVID-19 and Diabetes Mellitus: A Life Threatening Reciprocal Association

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Received: 16 September 2021 / Received in revised form: 07 December 2021, Accepted: 16 December 2021, Published online: 19 December 2021

### Abstract

COVID-19 storm has taken the world and is now posing a massive burden on the healthcare services of the world. Another long-standing global epidemic is diabetes mellitus and diabetics who get infected with COVID-19 have been seen to have worse outcomes and a high non-survival rate. The global focus is to control the pandemic for which diabetes has been proved to be a vulnerable group. The aim of the present review was to assemble the information about diabetes mellitus and COVID-19 mainly focusing on the interrelation of pandemics of the past and diabetes mellitus, possible pathophysiological mechanisms governing COVID-19 in diabetics, the effect of COVID-19 infection on underlying diabetes mellitus, morbidity, and mortality in diabetic COVID-19 patients, and finally the management of Diabetes Mellitus (DM) in the current pandemic. It was concluded that this COVID-19 pandemic is still lurking and it is of great importance to highlight the fact that a high percentage of the population of the world is affected by various comorbidities like diabetes mellitus, hypertension, COPD, obesity, etc., which makes a subset of the population more vulnerable. This vulnerable population is at increased risk for a poor outcome if affected by COVID-19. Hence, we as a society should prioritize this population at risk to avoid adding additional burden to the already overburdened health care system in the present COVID-19 scenario.

**Keywords:** COVID-19, SARS Cov 2, Diabetes mellitus, Health care services

### Introduction

COVID-19 storm has taken the world and is now posing a massive burden on the healthcare services of the world (Siyal *et al.*, 2020). The alleged epicenter of COVID-19 is Wuhan, China from where it is known to have originated and spread (Fadel & Ahmed, 2020). As of 20<sup>th</sup> January 2021, there have been 100,422,489 COVID-19 infected cases and 2,153,587 deaths due to COVID-19 worldwide. Recent studies show that diabetes mellitus, hypertension, cardiovascular diseases, and Chronic Obstructive Pulmonary Disease (COPD) are the comorbidities commonly present in COVID-19 patients and are responsible for an unfavorable outcome (Guan *et al.*, 2020; Lian *et al.*, 2020).

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Another long-standing global epidemic is diabetes mellitus. According to the International Diabetes Federation, presently there are 463 million diabetics in the world, which poses an expenditure burden of USD 760 billion on health services of all parts of the world (International Diabetes Federation, 2019). Diabetics who get infected with COVID-19 have been seen to have worse outcomes and a high non-survival rate (Pal & Bhadada, 2020). The global focus is to control the pandemic for which diabetes has been proved to be a vulnerable group.

### Aim

The aim of the present review is to assemble the information about diabetes mellitus and COVID-19. It mainly focuses on the interrelation of pandemics of the past and diabetes mellitus, possible pathophysiological mechanisms governing COVID-19 in diabetics, the effect of COVID-19 infection on underlying diabetes mellitus, illness, and fatality in COVID-19 patients with suffering from diabetes, and finally the management of DM in the current pandemic.

### Materials and Methods

A literature search was done in the Google Scholar and PubMed database using the keywords COVID-19 and DM. Information in the published articles was included in the present review. The updated data pertaining to DM and COVID-19 was taken from the official websites of the World Health Organization (WHO), International Diabetes Federation (IDF), and Centers for Disease Control and Prevention (CDC). This survey study is updated until writing time, which however might change at a later date as the data is still evolving.

### *Interrelation of the Acute Viral Pandemics of the Past and Diabetes Mellitus*

The long term complications related to DM is associated with diminished immune responses. This increases mortality and morbidity in case of acute infections. Previous studies have documented that HbA1c levels greater than 9%, have been associated with critical pneumonia and acute hospitalization in case of bacterial infections. Diabetes was also associated with complications during the prevalence of Severe Acute Respiratory Syndrome (SARS Cov 1) during 2002-2003 (Allard *et al.*, 2010). In addition, a higher degree of risk for ICU admission was seen in diabetics during influenza (H1N1) infection prevalence in 2009. Similarly, within the 2012 Middle East Respiratory Syndrome coronavirus outbreak, a morbidity rate of as high as 35% was seen



in diabetics (Al-Tawfiq *et al.*, 2014; Alraddadi *et al.*, 2016; Badawi & Ryoo, 2016).

#### *Possible Patho-Physiological Mechanisms Governing Covid-19 in Diabetes Mellitus*

Recent updates in studies have supported the preconceived idea that COVID-19 infection in diabetics can lead to severe complications with an increased risk of admission to ICU, need for ventilator support, and death. However, the severity cannot be predicted on the basis of the type of diabetes and that poor prognosis is seen in both type 1 and type 2 diabetes (Jafar *et al.*, 2016).

There are various possible pathophysiological mechanisms that can be used to support the interrelationship of DM and COVID-19 intensity. It has been seen that diabetic COVID-19 patients have a significantly higher level of IL 6, CRP, and ferritin in comparison to COVID-19 patients without DM. This suggests that COVID-19 patients with DM are more sensitive to an exaggerated cytokine response. This could lead to shock, acute respiratory distress, and rapid deterioration in the stability of the COVID-19 patient (Guo *et al.*, 2020).

Moreover, it has been documented that the D-dimer levels are higher in the diabetic COVID-19 patients. This highlights the fact the hemostatic mechanism is already in an activated state in diabetic individuals. This prothrombotic hypercoagulable state can lead to serious thromboembolic complications hence reducing the chances of recovery and survival (Hussain *et al.*, 2020).

It is also of importance that the functioning of the innate immune system, which is the first line of defense against infections like SARS COV 2, is compromised in uncontrolled type 2 DM.

Additionally, there is decreased expression of Angiotensin-converting enzyme 2 (ACE 2) in diabetes mellitus. Studies have shown that ACE 2 has a protective role against the avian influenza H5N1 infection. Therefore, low expression of ACE in diabetes mellitus explains the intense lung damage and ARDS with COVID-19 (Tikellis & Thomas, 2012; Zou *et al.*, 2014).

ACE inhibitors and Angiotensin Receptor Blockers (ARBs) are utilized as antihypertensive drugs especially in diabetics. There is an enhanced expression of ACE 2 by the use of drugs based on the aforementioned mechanism. The SARS Cov 2 virus uses ACE 2 as a recipient for entrance into the host pneumocytes. Therefore, adjustment of ACE facilitates the entry followed by multiplication of the coronavirus. However, as soon as the virus enters the host cell via the ACE, the ACE 2 gets down-regulated and is now incapable to defend against severe lung damage (Cure & Cure, 2020).

Another theory states that the nonstructural proteins of the SARS CoV 2 attacks the beta chain of hemoglobin, resulting in uncoupling of the iron atom from the porphyrin ring. This in turn decreases the oxygen-carrying capacity of hemoglobin (Wenzhong & Hualan, 2020).

## Results and Discussion

### *The Effect of Covid-19 Infection on Underlying Diabetes Mellitus*

It was reported by Yang *et al.* that patients suffering from SARS, resulted by SARS CoV (same family as SARS Cov 2) had a higher fasting plasma glucose and worsening of glycemic control in comparison to patients with non-SARS pneumonia. This could be described by the damage of the pancreatic beta cells by the SARS CoV virus as the ACE 2 receptors are also expressed on the pancreatic islets. In addition, studies showed that SARS CoV was also identified in the pancreas of patients who died due to SARSCoV (Ding *et al.*, 2004; Yang *et al.*, 2006; Yang *et al.*, 2010).

Moreover, COVID-19 can increase insulin resistance by induction of a pro-inflammatory state. Furthermore, obesity, which is commonly present in type 2 diabetes mellitus can further stimulate the cytokine response, that further decreases insulin sensitivity (Wan *et al.*, 2006; Kassir, 2020).

COVID-19 is also linked to down-regulation of ACE 2 receptors in the lungs thereby reduced degradation of Angiotensin 2 and increased aldosterone secretion. This leads to hypokalemia that worsens the glycemic control in diabetic patients (Liamis *et al.*, 2014; Pal & Bhadada, 2020).

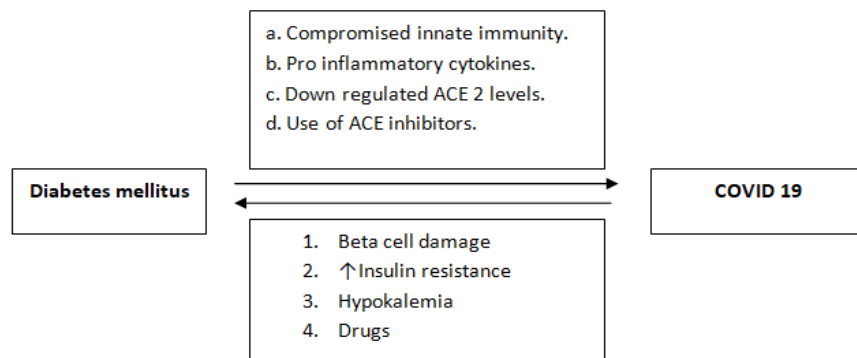
COVID-19 outbreak has led to nationwide lockdowns, which has reduced outdoor activity. This leads to reduced exposure to sunlight, which has added to vitamin D deficiency already prevalent in the population. As vitamin D increases insulin sensitivity, its shortage can result in aggravating the glycemic status in diabetics (Szymczak-Pajor & Śliwińska, 2019; Carter *et al.*, 2020).

Additionally, the medicines consumed for treatment of ARDS and sepsis of COVID-19 patients have an indirect effect on the glycemic status of the diabetic COVID-19 patients. Some drugs like corticosteroids, Ritonavir/Lopinavir, Azithromycin, and Interferon-beta 1 have a hyperglycemic effect whereas others like chloroquine, Tocilizumab showed an improvement in glucose profile (**Table 1**) (Nakamura *et al.*, 2011; Chou *et al.*, 2013; Epperla & McKiernan, 2015; Gautret *et al.*, 2020; Sallard *et al.*, 2020).

All these factors show that COVID-19 in diabetic patients results in exacerbation of glycemic control, which further compromises the existing immunity with the spawning of pro-inflammatory cytokines there with generating a ferocious cycle (**Figure 1**).

**Table 1.** Metabolic Effects of Drugs Utilized for Treatment of COVID-19

Drugs	Function of drugs	Impact on glycemic status	Impact on Lipid profile
Corticosteroids	Anti-inflammatory	Hyperglycemia	Enhancement in TC, LDL, TG
Ritonavir/ Lopinavir	Protease inhibitors	Hyperglycemia	Increase in TC, TG
Azithromycin	Macrolide antibiotic	Variable effect	Unspecified
Tocilizumab	Monoclonal antibody against IL-6	Better glucose profile	Increase in TC, HDL, TG, no change in LDL
Chloroquine	Inhibits viral entry and immunomodulator	Modifies glucose profile	Decrease in TC, LDL, TG
Interferon-beta 1	Adaptive immune response stimulator	Causes autoimmune $\beta$ -cell damage that leads to hyperglycemia.	Increase in TG



**Figure 1.** Reciprocal Interplay between COVID-19 and Diabetes Mellitus

*Morbidity and Mortality in Diabetic Covid-19 Patients*

Recently published data shows that COVID-19 patients with diabetes have a worse outcome when compared to nondiabetic COVID patients. In addition, more COVID admissions are recorded in patients with comorbidities especially diabetes mellitus.

In the study conducted in the United States, Bhatraju *et al.* showed that 58% of the total number of the COVID-19 subjects had diabetes mellitus (Bhatraju *et al.*, 2020). Other studies, mainly conducted in Italy showed the presence of diabetes mellitus in 33-

36% of COVID-19 patients (Onder *et al.*, 2020). Most of the studies were carried out in China where the percentage of COVID-19 patients with diabetes ranged from 5 to 20% (Table 2). Additionally, the number of admissions in ICU was more for COVID-19 with diabetes in comparison to non-diabetic COVID-19 patients. Moreover, most of the non-survivor COVID-19 patients were documented to be diabetic (Table 3) (Chen *et al.*, 2020; Guan *et al.*, 2020; Guo *et al.*, 2020; Huang *et al.*, 2020; Liu *et al.*, 2020; Wang *et al.*, 2020; Wu *et al.*, 2020; Yang *et al.*, 2020; Zhang *et al.*, 2020; Zhou *et al.*, 2020).

**Table 2.** Prevalence of Diabetes Mellitus in COVID-19 Patients

First author of the Study	Total No. of patients	% of patients with Diabetes
<b>COVID-19 in China</b>		
Liu <i>et al.</i> (2020)	61	8.2
Guo <i>et al.</i> (2020)	187	15
Wu <i>et al.</i> (2020)	201	10.9
Yang <i>et al.</i> (2020)	52	17
Zhang <i>et al.</i> (2020)	140	12.1
Zhou <i>et al.</i> (2020)	191	19
Wang <i>et al.</i> (2020)	138	10.1
Chen <i>et al.</i> (2020)	99	12.1
Huang <i>et al.</i> (2020)	41	19.5

Guan <i>et al.</i> (2020)	1099	7.4
<b>COVID-19 in Italy</b>		
Onduet <i>et al.</i> (2020)	355	35.5
<b>COVID-19 in USA</b>		
Bhatraju <i>et al.</i> (2020)	24	58

**Table 3.** Outbreak of Severe versus Non-severe and Survivor versus Non-survivor Diabetic COVID-19 Patients

First author of the Study	Total no. of patients	% of patients with Diabetes	Non-severe (Non ICU care) (% of total)	Severe (ICU care) (% of total)	Diabetic Survivors of COVID-19 (% of total)	Diabetic Non-Survivors of COVID-19 (% of total)
Liu <i>et al.</i>	61	8.2	4.5%	17.6%	NR	NR
Guan <i>et al.</i>	1099	7.4	5.7%	16.2%	6.1%	26.9%
Wu <i>et al.</i>	201	10.9	5.1%	19%	12.5%	25%
Zhou <i>et al.</i>	191	19	NR	NR	14%	31%
Yang <i>et al.</i>	52	17	NR	NR	22%	10%
Huang <i>et al.</i>	41	19.5	8%	25%	NR	NR

NR- Not reported in the study

#### Management of Diabetes Mellitus in the Current Covid-19 Pandemic and How Can Society Help

The pandemic is still out there and there is no stopping till there is the development of herd immunity or mass vaccination. In the absence of definitive therapy, unavailability of beds in the ICUs, slow phase-in of vaccinations; it is of utmost importance that individual with diabetes mellitus follow necessary precautions like physical distancing, hand hygiene, and use of alcohol-based hand rubs/wipes. However, reduced outdoor exposure would lead to hindrance in their regular health check-up, physical activity, and psychological health (Winchester *et al.*, 2016; Mukhtar & Mukhtar, 2020).

Adhering to this requirement, telemedicine has been made available at most hospitals where patients would be able to consult their registered medical practitioner telephonically or on a digital platform. Many digital platforms are broadcasting regular exercise routines that can be tailored according to personal capacity (Ghosh *et al.*, 2020; Iacobucci, 2020). Neighbors and friends of diabetic individuals are being encouraged by government officials to help this vulnerable population. Help from the local population would help in the reduction of the 'supermarket shopping time'. The IDF has recommended that diabetic individuals keep an adequate stock of medication, an instrument for blood glucose monitoring, and have a healthy diet laden with protein, fiber, vitamins, minerals, and limited saturated fats (Banerjee *et al.*, 2020).

#### Conclusion

This COVID-19 pandemic is still lurking. It is of great importance to highlight the fact that a high percentage of the population of the world is affected by various comorbidities like diabetes mellitus, hypertension, COPD, obesity, etc., which makes a subset of the population more vulnerable. This vulnerable population is at increased risk for a poor outcome if affected by COVID-19 (Fadel

& Ahmed, 2020; Fang *et al.*, 2020; Siyal *et al.*, 2020; Xue *et al.*, 2020).

Hence, we as a society should give more attention to this population at risk to avoid adding additional burden to the already overburdened health care system in the present COVID-19 scenario.

**Acknowledgments:** All the authors duly acknowledge the support of the management of Santosh deemed to be University-Ghaziabad.

**Conflict of interest:** None

**Financial support:** The study was supported by the Department of Biochemistry, Santosh Medical College-Ghaziabad.

**Ethics statement:** None

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