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Covid-19 and Diabetes Mellitus: A Life-Threatening Reciprocal Association

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Abstract

COVID-19 has taken the world by storm and is now posing as 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 proved to be a vulnerable group. The present review aimed 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 in the current pandemic.it is 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, Co morbidities, CVD

Introduction

COVID-19 has taken the world by storm and is now posing as a massive burden on the healthcare services of the world. The alleged epicenter of COVID-19is Wuhan, China, from where it is known to have originated and spread (Magomedova *et al.*, 2020; Siyal *et al.*, 2020). As of 20th January 2021, there have been 100,42,2489 COVID-19 infected cases and 2,15,3587 deaths due to COVID-19 worldwide. Recent studies show that Diabetes mellitus, hypertension, cardiovascular diseases, and Chronic obstructive pulmonary disease (COPD) are the co morbidities commonly present in COVID-19patients 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 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 proved to be a vulnerable group.

Aim

The present review aims 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, morbidity, and mortality in diabetic COVID-19 patients, and finally the management of Diabetes mellitus in the current pandemic.

Materials and Methods

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

Results and Discussion

The interrelation of the Acute Viral Pandemics of the Past and Diabetes Mellitus

The long-term complications associated with Diabetes mellitus are associated with diminished immune responses. This increases mortality and morbidity in the case of acute infections (Akbar, 2001) 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 outbreak of Severe Acute Respiratory Syndrome (SARS Cov 1) during 2002-2003 (Yang *et al.*, 2006; Allard *et al.*, 2010). Also, a higher degree of risk for ICU admission was seen in Diabetics during Influenza (H1N1)

infection outbreak in 2009. Similarly, during 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 Pathophysiological 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 based on the type of diabetes and that poor prognosis is seen in both; Type 1 and Type 2 diabetes (Jafar *et al.*, 2016).

Various possible pathophysiological mechanisms can be used to support the interrelationship of Diabetes mellitus and COVID-19 severity. It has been seen that diabetic COVID-19patients have a significantly higher level of IL 6, CRP, and ferritin when compared to COVID-19 patients without Diabetes mellitus. This suggests that COVID-19 patients with Diabetes mellitus are more susceptible 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).

Also, it has been documented that the D dimer levels are higher in diabeticCOVID-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 Diabetes mellitus.

Additionally, there is reduced 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 severe lung injury and ARDS with COVID-19 (Zou *et al.*, 2014; Tikellis & Thomas, 2012).

ACE inhibitors and Angiotensin receptor blockers (ARBs) are used as antihypertensive drugs especially in diabetics. There is an increased expression of ACE 2 by the use of drugs based on the aforementioned mechanism. The SARS-Cov-2 virus uses ACE 2 as a receptor for entry into the host pneumocytes. Thus, upregulation of ACE facilitates the entry followed by proliferation of the coronavirus. However, once the virus enters the host cell via the ACE, the ACE 2 gets down-regulated and is now unable to protect against acute lung injury (Cure & Cure, 2020).

Another theory states that the non-structural proteins of the SARS-Cov-2attack the beta chain of hemoglobin, leading to the uncoupling of Iron atoms from the porphyrin ring. This in turn decreases theoxygen-carrying capacity of hemoglobin (Liu & Li, 2020).

Effect of COVID-19Infection on Underlying Diabetes Mellitus

It was reported by Yang *et al.* that patients suffering from SARS, caused due to SARS CoV (same family as SARS-Cov-2) had a higher fasting plasma glucose and worsening of glycemic control when compared to patients with non-SARS pneumonia. This could be explained 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. Also, studies showed that SARS CoV was also identified in the pancreas of patients who died due to SARS CoV (Yang *et al.*, 2006; Yang *et al.*, 2010).

Additionally, COVID-19 can increase insulin resistance by induction of a pro-inflammatory state. Also, 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-19has also been linked to the down regulation of ACE 2 receptors in the lungs thereby reduced the 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 lead 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 deficiency can lead to worsening of the glycemic status in diabetic patients (Szymczak-Pajor & Śliwińska, 2019; Carter *et al.*, 2020).

Also, the drugs used in the management 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, 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 leads to exacerbation of glycemic control which further compromises the existing immunity with the spawning of pro-inflammatory cytokines thereby generating a ferocious cycle **(Figure 1)**.

Table 1**.** Metabolic Effects of Drugs Used in the Management of COVID-19.

Drugs	Mechanism of action of drugs	Effect on glycemic status	Effect on Lipid profile
Corticosteroids	Anti-inflammatory	Hyperglycemia	Increase 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	Improves glucose profile	Increase in TC, HDL, TG, no change in LDL
Chloroquine	Prevents viral entry and immunomodulator	Improves glucose profile	A decrease in TC, LDL, TG
Interferon-beta 1	Adaptive immune response stimulator	Causes autoimmune b -cell damage that leads to hyperglycemia.	Increase in TG

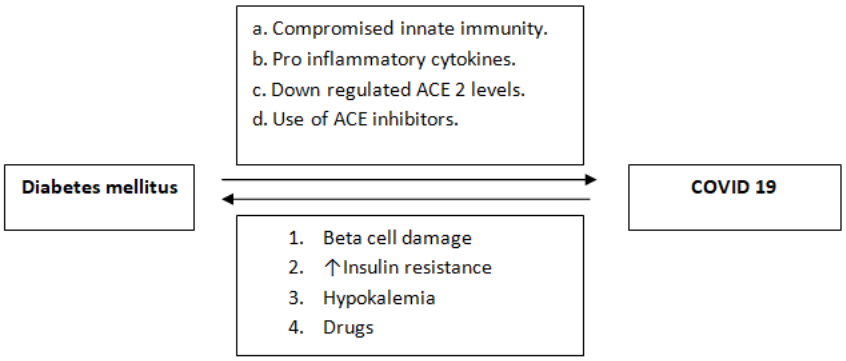

Figure 1. Reciprocal interaction between COVID-19 and Diabetes mellitus.

Morbidity and Mortality in Diabetic COVID-19Patients

Recently published data shows that COVID-19 patients with diabetes have a worse outcome when compared to non-diabetic COVID patients. Also, more COVID admissions are recorded in patients with co morbidities 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 conducted in China where the percentage of COVID-19 patients with diabetes ranged from 5-20% **(Table 2)**. Additionally, the number of admissions in ICU was more for COVID-19 with diabetes when compared to non-diabeticCOVID-19 patients. Also, most of the non-survivorCOVID-19 patients were documented to be diabetic **(Table 3) (**Chen *et al.*, 2020; Fu *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-19Patients.

First author of the Study	Total no. of patients	% of patients with Diabetes
COVID-19 in China		
Liu *et al.* (2020)	61	8.2
Guo *et al.* (2020)	187	15
Wu *et al.* (2020)	201	10.9
Yang *et al.* (2020)	52	17
Zhang *et al.* (2020)	140	12.1
Zhou *et al.* (2020)	191	19
Wang *et al.* (2020)	138	10.1
Chen *et al.* (2020)	99	12.1
Huang *et al.* (2020)	41	19.5
Guan *et al.* (2020)	1099	7.4
COVID-19 in Italy		
Ondu *et al.* (2020)	355	35.5

COVID-19 in the USA		
Bhatraju *et al.* (2020)	24	58

Table 3. Prevalence 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 *et al.*	61	8.2	4.5%	17.6%	NR	NR
Guan *et al.*	1099	7.4	5.7%	16.2%	6.1%	26.9%
Wu *et al.*	201	10.9	5.1%	19%	12.5%	25%
Zhou *et al.*	191	19	NR	NR	14%	31%
Yang *et al.*	52	17	NR	NR	22%	10%
Huang *et al.*	41	19.5	8%	25%	NR	NR

NR- Not reported in the study

Management of Diabetes Mellitus in the Current COVID-19Pandemic and How can Society Help.

The pandemic is still out there and there is no stopping till there is a 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 individuals 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 (Banerjee *et al.*, 2020; Ghosh *et al.*, 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, fibre, vitamins, minerals, and limited saturated fats (Banerjee *et al.*, 2020).

Conclusion

TheCOVID-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 co morbidities 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 (Fang *et al.*, 2020; Pal & Bhadada, 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-19scenario.

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Conflict of interest: None

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Ethics statement: This article is a review of the articles published pertaining to Covid 19 in Diabetes mellitus patients for which due citation has been given and permission taken from Institutional Ethics Committee.

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