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# Managing Diabetes in COVID-19 patients: Evidence based Clinical Review

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**ABSTRACT:** Diabetes Mellitus is suggested as a risk factor which contributes to the severity and mortality of COVID-19. Several factors in COVID-19 infection like the impaired immune response, heightened inflammatory response and hypercoagulable state contribute to the increased disease severity. Diabetes is chronic conditions with devastating multi-systemic complications. Understanding how diabetes affects COVID-19 severity is critical to designing tailored treatments and clinical management of individuals affected by diabetes. This research paper aims to discuss pathophysiology of Diabetes and Covid-19 infection and highlight importance of Self-management of Diabetes by Telemedicine support and treatment by both insulin and non-insulin agents.

**Keywords-**Diabetes Mellitus, Diabetic Ketoacidosis (DKA), Hyperglycemic Hyperosmolar Syndrome (HHS), Coronavirus disease -2019 (COVID-19), angiotensin-converting enzyme 2 (ACE2), SARS-CoV-2(severe acute respiratory syndrome-coronavirus -2).

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## I. INTRODUCTION

This research paper discusses latest evidence-based practices in learning about pathophysiology of severity of Diabetes in COVID-19 infections and how to manage diabetes by community support provided by Telemedicine to better self-monitor sugar levels and associated complications. In addition to this we discuss both Non-Insulin and Insulin based strategies. This paper also discusses latest evidence-based research in preventing Diabetic Ketoacidosis(DKA), Hypoglycemia andHHS (hyperglycemic hyperosmolar syndrome).

### Diabetes as risk factor for COVID-19

**Tadic et al., (2020)**notes in their research thatthe pandemic of COVID-19, a disease caused by a novel coronavirus SARS-CoV-2, is associated with significant morbidity and mortality. Recent data showed that hypertension, diabetes mellitus, cardiovascular diseases, and chronic obstructive pulmonary disease were the most prevalent comorbidities in COVID-19 patients. Additionally, data indicate that hypertension, diabetes, and cardiovascular diseases are important risk factors for progression and unfavourable outcome in COVID-19 patients.

**Kumar et al., (2020)**stated thatmany studies on COVID-19 have reported diabetes to be associated with severe disease and mortality. In their research they showed thatdiabetes in patients with COVID-19 is associated with a two-fold increase in mortality as well as severity of COVID-19, as compared to non-diabetics.

**Huang et al., (2020)**also investigated the association between DM and poor outcome in patients with COVID-19 pneumonia. Their conclusion was that DM was associated with mortality, severe COVID-19, ARDS, and disease progression in patients with COVID-19.

**Abdi et al., (2020)**stated thatCOVID-19 pneumonia is a newly recognized illness that is spreading rapidly around the world and causes many disability and deaths. Some diseases, for instance diabetes, is continuously suggested as a risk factor which contributes to the severity and mortality of COVID-19 and that it is likely that diabetic patients will be treated with antibiotics, antivirals, and HCQ (hydroxychloroquine).

**Ejaz et al., (2020)**discussed the effect of comorbidities like diabetes on COVID-19 patients**.** SARS-CoV-2 utilizes ACE-2 receptors found at the surface of the host cells to get inside the cell. Certain comorbidities are associated with a strong ACE-2 receptor expression and higher release of proprotein convertase that enhances the viral entry into the host cells. The comorbidities lead to the COVID-19 patient into a vicious infectious circle of life and are substantially associated with significant morbidity and mortality. The comorbid individuals must adopt the vigilant preventive measure and require scrupulous management.

**Dennis et al., (2021)**discussed the relationship between type 2 diabetes and all-cause

mortality among adults with coronavirus disease 2019 (COVID-19) in the critical care setting. Patients with type 2 diabetes were at increased risk of death, and this result was consistent in HDU and ICU subsets. The relative mortality risk associated with type 2 diabetes decreased with higher age (age 18–49 years).

**Ren et al., (2020)**mentioned novel concept ofthe triglyceride and glucose index (TyG) as a marker of insulin resistance. Their study evaluated the association of the TyG index with the severity and mortality of coronavirus disease 2019 (COVID-19). TyG index was closely associated with the severity and morbidity in COVID-19 patients, thus it may be a valuable marker for identifying poor outcome of COVID-19.

**Pathophysiology of Diabetes and Covid -19 complications**

**Hussain et al., (2020)** aimed to briefly review the general characteristics of the novel coronavirus (SARS-CoV-2) and provide a better understanding of the coronavirus disease (COVID-19) in people with diabetes, and its management. They proposed that chronic inflammation, increased coagulation activity, immune response impairment, and potential direct pancreatic damage by SARS-CoV-2 might be among the underlying mechanisms of the association between diabetes and COVID-19. They concluded that further research regarding this relationship and its clinical management is warranted.

**Erener et al., (2020)**stated pathophysiological mechanism likecytokine storm, pulmonary and endothelial dysfunction, and hypercoagulation, may render individuals with diabetes more vulnerable to COVID-19. This will help to understandhow diabetes affects COVID-19 severity and how to design tailored treatments and clinical management of individuals affected by diabetes.

**Pal et al., (2020)**discuss the concept of vicious cycle between diabetes and COVID-19 infection**.** Diabetes mellitus is associated with poor prognosis in patients with COVID-19. On the other hand, COVID-19 contributes to worsening of dysglycemia in people with diabetes mellitus over and above that contributed by stress hyperglycemia. Compromised innate immunity, pro-inflammatory cytokine milieu, reduced expression of ACE2 and use of renin-angiotensin-aldosterone system antagonists in people with diabetes mellitus contribute to poor prognosis in COVID-19. On the contrary, direct β-cell damage, cytokine-induced insulin resistance, hypokalemia and drugs used in the treatment of COVID-19 (like corticosteroids, lopinavir/ritonavir) can contribute to worsening of glucose control in people with diabetes mellitus.The two-way interaction between COVID-19 and diabetes mellitus sets up a vicious cycle wherein COVID-19 leads to worsening of dysglycemia and diabetes mellitus, in turn, exacerbates the severity of COVID-19. Thus, it is imperative that people with diabetes mellitus take all necessary precautions and ensure good glycemic control amid the ongoing pandemic.

**Cuschieri et al., (2020)**stated that thediabetes population suffers adverse outcomes if infected by COVID-19.COVID-19 may enhance complications in individuals with diabetes through an imbalance in angiotensin-converting enzyme 2 (ACE2) activation pathways leading to an inflammatory response. ACE2 imbalance in the pancreas causes acute β-cell dysfunction and a resultant hyperglycemic state. These individuals may be prone to worsened COVID-19 complications including vasculopathy, coagulopathy as well as psychological stress. Apart from general preventive measures, remaining hydrated, monitoring blood glucose regularly and monitoring ketone bodies in urine if on insulin is essential. All this while concurrently maintaining physical activity and a healthy diet. Different supporting entities are being set up to help this populationspecial attention during this pandemic to avoid adding on to the burden of countries' healthcare systems.

**Gupta et al., (2020)**also mentioned that thePatients with diabetes who get coronavirus disease 2019 (COVID-19) are at risk of a severe disease course and mortality. Several factors especially the impaired immune response, heightened inflammatory response and hypercoagulable state contribute to the increased disease severity.

**Muniangi-Muhitu et al., (2020)**Covid-19 is a recently-emerged infectious disease caused by the novel severe acute respiratory syndrome coronavirus SARS-CoV2. SARS-CoV2 differs from previous coronavirus infections (SARS and MERS) due to its high infectivity (reproduction value, $R_0$, typically 2-4) and pre- or asymptomatic transmission, properties that have contributed to the current global Covid-19 pandemic.Evidence is also emerging that SARS-CoV2 infection exacerbates the underlying pathophysiology of hyperglycemia in people with diabetes. Here, we discuss potential mechanisms through which diabetes may affect the risk of more severe outcomes in Covid-19 and, additionally, how diabetic emergencies and longer-term pathology may be aggravated by infection with the virus. We consider roles for the immune

system, the observed phenomenon of microangiopathy in severe Covid-19 infection and the potential for direct viral toxicity on metabolically-relevant tissues including pancreatic beta cells and targets of insulin action.

**SMBG (self-monitoring of blood glucose) and Telemedicine**

**Peric et al., (2020)** stated importance of adopting novel ways to support diabetes patients in pandemic**.** Diabetes mellitus predisposes to a particularly severe course of the disease and doubles the COVID-19 mortality risk due to pulmonary and cardiac involvement. Glycemic control during infectious diseases is often suboptimal, and antidiabetic drugs and insulin therapy have to be adapted accordingly. On the other hand, access of diabetes patients to outpatient clinics are limited during the ongoing season urging alternative treatment options, particularly the implementation of novel telemedicine strategies. Hence, the opportunity of the COVID 19 crisis should be taken to make a significant step forward in the care for diabetes patients.

**Banerjee et al., (2020)** have reemphasized the need for a simultaneous patient-centred approach in routine diabetes care that has to be coordinated by a multidisciplinary team amid the ongoing COVID-19 pandemic. They discussed an educational plan on diabetes self-management that can be adopted for people with diabetes mellitus.

**Non-Insulin treatment**

**Chen et al., (2020)** described the clinical characteristics and outcomes in patients with diabetes in whom COVID-19 was confirmed or clinically diagnosed (with typical features on lung imaging and symptoms) and their association with glucose-lowering or blood pressure–lowering medications. It was a retrospective study involving 904 patients with COVID-19 (136 with diabetes, mostly type 2 diabetes). The study showed that C-reactive protein may help to identify patients with diabetes who are at greater risk of dying during hospitalization. Older patients with diabetes were prone to death related to COVID-19. Attention needs to be paid to patients with diabetes and COVID-19 who use insulin. ACEI/ARB use showed no significant impact on patients with diabetes and hypertension who have COVID-19.

**Bramante et al., (2020)** in their study aimed to identify whether metformin reduced mortality from Covid19 and if sex specific interactions exist. The study showed that Metformin was significantly associated with reduced mortality in women with obesity or T2DM hospitalized with Covid-19. This sex-specific finding is consistent with metformin's reduction of TNFα in females over males, and suggests that metformin conveys protection in Covid-19 through TNFα effects. Prospective studies are needed to understand mechanism and causality.

**Solerte et al., (2020)** in theirmulticenter, case-control, retrospective, observational study, showed that, sitagliptin treatment at the time of hospitalization was associated with reduced mortality and improved clinical outcomes as compared with standard-of-care treatment in diabetes type 2 patients. They advised that the effects of sitagliptin in patients with type 2 diabetes and COVID-19 should be confirmed in an ongoing randomized, placebo-controlled trial.

**Fang et al., (2020)** in their study describeda patient who developed euglycaemic diabetic ketoacidosis (DKA) in the setting of SGLT2 inhibitor use precipitated by COVID-19. Clinicians should be cognizant that the effects of SGLT2 inhibitors can persist for more than 72 hours after the last dose. Diabetic patients with COVID-19 require closer strict glucose monitoring to reduce the risk of DKA.

**Shah et al., (2020)** in their study warned about common causes of hypoglycemia. A combination of Metformin and Sulfonylureas (SU) was most commonly associated with the risk of hypoglycemia (65.75%) followed by insulin (33.56%). The COVID-19 lockdown has shown to influence the risk of hypoglycemia in patients with T2DM, especially those receiving SU, insulin, HCQ especially in patients with associated co-morbidities. Patient education, support, and telemedicine plays a pivotal role to prevent hypoglycemia

**Singh et al., (2020)** reported in their review article the outcomes of non-insulin anti-diabetic agents (ADA) in patients with T2DM and coronavirus disease 2019 (COVID-19). Their conclusion was that Metformin and DPP-4i (gliptins) should be continued in patients with T2DM until hospitalization or unless contraindicated. No evidence of harm suggests that SUs, SGLT-2i or GLP-1RAs may not be stopped unless very sick, hospitalized or contraindicated.

**Insulin treatment**

**Marazuela et al., (2020)** described risk associated with diabetes and obesity in COVID-19 patients**.** Diabetes and/or obesity, the coexistence of these conditions contributes to a worse prognosis

because both conditions confer an impaired immunologic system. Cytokines storm can be amplified by these two latter conditions thereby leading to multisystemic failure and death. Glycaemic control has been demonstrated to be crucial to avoiding long hospital stays, ICU requirement and also prevention of excessive mortality. Endocrine treatment modifications as a consequence of COVID-19 infection are required in a proactive manner, in order to avoid decompensation and eventual hospital admission. This is the case of diabetes and adrenal insufficiency in which prompt increase of insulin dosage and substitutive adrenal steroids through adoption of the sick day's rules should be warranted, as well as easy contact with the health care provider through telematic different modalities.

**Cariou et al., (2020)** in theirCORONADO (CORONAvirus SARS-CoV-2 and Diabetes Outcomes) study confirmed that diabetes was associated with an increased risk of in-hospital death. They found that older age and elevated CRP were independently associated with in-hospital death in patients with diabetes. It is becoming increasingly evident that elevated admission plasma glucose is a marker of severe COVID-19 prognosis. The study also demonstrated that previous glucose control assessed by A1C before admission was not associated with a worse COVID-19 prognosis.

**Yu et al., (2021)** stated that COVID-19 caused by SARS-COV-2 infection can lead to multi-organ injuries and significant mortality in severe and critical patients, especially among those individuals with type 2 diabetes (T2D) as a comorbidity. While attenuated mortality was observed with aggressive glucose control, it was unclear whether therapeutic regimens including insulin treatment were beneficial for patients with COVID-19 and T2D. Unexpectedly they found that insulin treatment for patients with COVID-19 and T2D was associated with a significant increase in mortality (27.2% versus 3.5%; adjusted HR, 5.38 [2.75-10.54]). Further analysis showed that insulin treatment was associated with enhanced systemic inflammation and aggravated injuries of vital organs. Therefore, insulin treatment for patients with COVID-19 and T2D should be used with caution.

**Palermo et al., (2020)** in their research observed thatwhile individuals with diabetes appear to be at similar risk for SARS-CoV-2 infection to those without diabetes, they are more likely to suffer severe consequences, including death. Diabetic ketoacidosis (DKA) is a common and potentially lethal acute complication of diabetes arising from a relative insulin deficiency, which occurs more often in those with type 1 diabetes and in the setting of moderate to severe illness. Early reports indicate that among patients with pre-existing diabetes, DKA may be a common complication of severe COVID-19 and a poor prognostic sign. They concluded that DKA management may require flexibility in the setting of COVID-19 due to important public health goals, such as preventing transmission to highest risk individuals, reducing healthcare worker exposure to infected patients, and preserving personal protective equipment. Evidence for alternative treatment strategies is explored, with special attention placed on treatment options that may be more relevant during the pandemic, including use of subcutaneous insulin therapy.

**Reddy et al., (2020)** pointed out that COVID-19 can precipitate DKA in a significant number of patients. DKA can occur in patients with pre-existing diabetes or newly diagnosed diabetes. As COVID-19 and diabetes are prevalent conditions, high degree of suspicion is required to diagnose DKA timely in order to improve the prognosis of COVID-19-related diabetic ketoacidosis.

**Pal et al., (2020)** analyzed clinical outcomes of COVID-19 patients with diabetic ketoacidosis (DKA) and combined DKA/HHS (hyperglycemic hyperosmolar syndrome). DKA in COVID-19 patients portends a poor prognosis with a mortality rate approaching 50%. Differentiating isolated DKA from combined DKA/HHS is essential as the latter represents nearly one-fifth of the DKA cases and tends to have higher mortality than DKA alone.

## II. CONCLUSION

Many studies on COVID-19 have reported diabetes to be associated with severe disease and mortality.The two-way interaction between COVID-19 and diabetes mellitus sets up a vicious cycle wherein COVID-19 leads to worsening of dysglycemia and diabetes mellitus, in turn, exacerbates the severity of COVID. This clinical review also highlighted how both insulin and non-insulin agents needs to be tailored for use in covid-19 infected diabetes patients. At the same time patient support by telemedicine is also valuable to avoid complications like hypoglycaemia and diabetic ketoacidosis (DKA).

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